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Results of an open label feasibility study of sodium valproate in people with McArdle disease

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Abstract

McArdle disease results from a lack of muscle glycogen phosphorylase in skeletal muscle tissue. Regenerating skeletal muscle fibres can express the brain glycogen phosphorylase isoenzyme. Stimulating expression of this enzyme could be a therapeutic strategy. Animal model studies indicate that sodium valproate (VPA) can increase expression of phosphorylase in skeletal muscle affected with McArdle disease. This study was designed to assess whether VPA can modify expression of brain phosphorylase isoenzyme in people with McArdle disease. This phase II, open label, feasibility pilot study to assess efficacy of six months treatment with VPA (20 mg/kg/day) included 16 people with McArdle disease. Primary outcome assessed changes in VO_2peak during an incremental cycle test. Secondary outcomes included: phosphorylase enzyme expression in post-treatment muscle biopsy, total distance walked in 12 min, plasma lactate change (forearm exercise test) and quality of life (SF36). Safety parameters. 14 participants completed the trial, VPA treatment was well tolerated; weight gain was the most frequently reported drug-related adverse event. There was no clinically meaningful change in any of the primary or secondary outcome measures including: VO_2peak, 12 min walk test and muscle biopsy to look for a change in the number of phosphorylase positive fibres between baseline and 6 months of treatment. Although this was a small open label feasibility study, it suggests that a larger randomised controlled study of VPA, may not be worthwhile.

Keywords: Glycogen storage disease type V; Sodium valproate (VPA); VO2peak; 12 min walking test; Outcome measures.

1. Introduction

McArdle disease is an autosomal recessive condition caused by mutations in the muscle glycogen phosphorylase gene (*PYGM*). Affected patients lack the enzyme muscle glycogen phosphorylase (MGP), which is essential for glycogen breakdown in skeletal muscles [1–4], which results in severe impairment of physical activity, especially when the onset of exercise is abrupt, high intensity or isometric in nature [5,6]. Currently, there is no satisfactory drug treatment for McArdle disease. Identifying new therapeutic strategies are therefore warranted [7].

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Mammals have three glycogen phosphorylase isoforms encoded by different genes that are tissue specific: muscle (MGP), liver (LGP) and brain (BGP) [8–10]. MGP, the exclusive form expressed in mature skeletal muscle fibres, is absent in people with McArdle disease due to recessively inherited mutations in the corresponding gene [9]. BGP is encoded by *PYGB* and is expressed in developing muscle tissue both *in vivo* and *in vitro*, and is thus transiently expressed in regenerating skeletal muscle fibres [11–14].

In-vitro studies on human primary skeletal muscle cell cultures derived from people with McArdle disease showed expression of BGP [13]. Such findings combined with knowledge of the normal physiological response to muscle damage (muscle regeneration) suggest that pharmaceutical reactivation of BGP in mature skeletal muscle fibres may be a therapeutic strategy for McArdle disease [13].

Sodium valproate (Valproic Acid, VPA) belongs to a group of drugs known as 'histone deacetylase (HDAC) inhibitors' that can activate the expression of methylated genes by increasing the accessibility of the demethylase enzyme to the DNA [15,16], A trial of VPA treatment in an ovine model of McArdle disease resulted in an increased number of glycogen phosphorylase positive skeletal muscle fibres, suggesting activation of BGP [17]. Encouraging results were also obtained in an *in vitro* knock-in (KI) mouse model of McArdle disease carrying the p.R50X mutation. Following VPA exposure, cultured myotubes from the mouse model expressed BGP in association with a dose-dependant decrease in muscle glycogen accumulation [18].

Based on this preclinical research, VPA could be considered as a potential therapeutic target for McArdle disease. This study was designed as a feasibility/pilot study to: a) determine whether or not VPA has an effect on BGP expression and b) to power a future randomised, placebo-controlled study (RCT).

2. Methods

The study was conducted at two sites: UCL Institute of Neurology, London, UK and Rigshospitalet, Copenhagen, Denmark. Protocol and study documents were approved by ethical committees and regulatory bodies for each site. Informed consent was obtained from all participants prior to any study procedures and the study was conducted in line with good clinical practice as determined by the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT03112889).

2.1. Study design

A phase II, open label, multi-centre feasibility study.

2.2. Participants

Based upon previous research in McArdle disease, it was anticipated that data from 16 participants would be adequate to provide a good estimate of the standard deviation of the change in the VO_2peak to inform the sample size calculation for a future RCT [19].

2.2.1. Inclusion criteria

All participants were over 18 years of age and diagnosed with GSDV (confirmed by DNA analysis for recessive mutations in *PYGM* and/or muscle biopsy showing subsarcolemmal blebs of glycogen and absence of skeletal muscle glycogen phosphorylase on histochemical stain. All participants (male and female) had to use contraception throughout the study unless they were post-menopausal or infertile.

2.2.2. Exclusion criteria

The following were exclusion criteria: pregnancy, diabetes, inflammatory disorders e.g.systemic lupus erythematosus, sensitivity/allergy to VPA, treatment with VPA within 12 months prior to recruitment, pre-existing liver disease or a family history of severe liver disease affecting a first degree relative, anti-convulsant medication or any other medication known to interact with VPA, sensitivity to local anaesthetics that would prevent muscle biopsy, any co-morbid illness or disability which would prevent an exercise assessment. Other metabolic condition affecting either the patient or a first-degree relative such as porphyria, mitochondrial disease, abnormal acyl carnitine profile or low serum carnitine

All participants received VPA extended release tablets (by Sanofi-Aventis) once daily. Participants were warned of the expected VPA related side-effects such as weight gain, fatigue, alterations in blood indices and risk of liver damage. VPA was introduced slowly with an escalating dose regimen with 5 mg/kg/day increments each week for three weeks up to the full dose treatment (20 mg/kg/day). This dose was chosen as it is the lowest recommended dose for treating epilepsy and we wanted to minimise known drug-related side-effects such as weight gain, drowsiness and thrombocytopenia that might outweigh any potential benefit. The daily dose was rounded up to the nearest available tablet strength and the maximum dose was 2 g/day. The ovine clinical trial conducted over 15 weeks showed an increase in the number of phosphorylase positive fibres over time [17]. We decided to treat our patients for 6 months, a longer time-period than the ovine trial, to maximise any potential positive impact. After six months on full dose treatment and after the final study visit, VPA dose was reduced by 5 mg/kg/day each week for three weeks and then discontinued.

2.3. Study visits

At screening, participants underwent a full medical history and examination. Investigations included ECG, laboratory blood tests for free carnitine, acyl carnitine profile, full blood count, liver and renal function. Participants performed an incremental baseline cycle test to determine exercise capacity.

Following screening, there were three study visits at week 0 (baseline – V1), week 16 (+−7 days – V2) and week 28 (+−7 days – V3). In between visits participants were telephoned every 4 weeks (+− 7 days) from baseline until week 40 to assess adverse events (AEs) and study compliance.

Assessment of Compliance. Compliance was also assessed at each study visit, and during telephone calls and returned pills were counted on V2 and V3. Compliance >90% was the minimum threshold for participants to continue in the trial.

2.4. Outcome measures

Screening visit cycle test: All participants exercised on a cycle ergometer. Oxygen consumption was assessed with the Cortex ergospirometry system (Cortex Metalyzer II, Cortex Biophysik GmbH, Leipzig, Germany) in the UK or Quark CPET (Cosmed Srl., Milan, Italy) in DK. An incremental cycle ergometer test was performed (from zero to 20 W in the first minute, increased by at least 5 W every two minutes) to determine each participant's aerobic capacity (VO_2peak).

2.4.1. Primary outcome

VO_2peak was measured in a constant-to-maximal workload cycle test on V1, V2 and V3. After fasting for four hours, participants cycled for 15 min at a constant workload at 65% of the VO_2peak determined in the screening test. After 15 min, the power output was increased by at least five watts every minute until maximal volition to determine the VO_2peak.

2.4.2. Secondary outcomes

a) *Muscle biopsy to assess number of phosphorylase positive fibres*: V1 and V3. Where available, recent diagnostic muscle biopsies of good quality undertaken prior to screening were used for analysis at baseline. The presence of phosphorylase was assessed using histochemistry and neonatal myosin staining was used to assess the presence of possible regenerating fibres. The histochemical method used identifies all isoforms of phosphorylase, given that the mutations in *PYGM* result in no phosphorylase expression, it was not considered necessary to include other methods to identify specific phosphorylase isoforms such as PCR. Muscle biopsy slides were scanned, and the number of glycogen phosphorylase muscle fibres were counted using ImageJ imaging software.

b) *Plasma lactate levels during a non-ischaemic forearm test: V1, V2, V3.* Repetitive maximal handgrip contractions using a hand-held dynamometer were performed every other second for one minute. Plasma lactate and serum ammonia levels were analysed at 0, 2 and 5 min.

c) *12-Minute Walk Distance (12MWD)*: V1, V2, V3 after 45 min of rest, following the cycle ergometer test. Participants were required to complete as many 10 m shuttle walks as possible for 12 min on a marked corridor. The total walked distance was analysed.

d) *Quality of life assessment: Short Form 36 (SF36 health survey)* V1, V2, V3 was completed and scored using the QualityMetric Health Outcomes™ Scoring Software.

e) *Safety measures:* All participants completed a symptom diary, which included: concomitant medications use, adverse events, myoglobinuria and significant worsening of McArdle symptoms information. The study team recorded adverse events at each visit and at frequent telephone calls. During V1, V2 and V3 safety blood analyses included: full blood count, CK, LFT, U&E, platelets, coagulation screen (PT, APTT, INR and fibrinogen), lactate, ammonia, glucose and VPA blood level.

f) *Adverse events were assessed.*

2.5. Statistical analysis

Due to the pilot nature of the study, the study was not powered to show statistically significant differences between treatment groups, and so all analysis was descriptive in nature. Summaries at each time point were produced, in addition to summaries of the changes from baseline to both V2 and V3. Changes from baseline were also calculated as a percentage of the baseline. Continuous variables were summarised by the mean and standard deviation and data range if found to follow a Normal distribution, and by the median and inter-quartile range, and data range if not normally distributed. Categorical variables were summarised by the frequency and percentage of values in each category.

The primary outcome was VO_2peak, measured during exercise on a cycle ergometer at maximum volition. Clinically important increases in VO_2peak and 12 min walk distance were predefined defined as greater than 10% of the baseline value. The clinical importance of any effects was compared to this fixed value.

We planned to use these data to provide an estimate of standard deviation of the change in each of these factors that would be required for the sample size calculation of a larger RCT in the future. Since exercise capacity in McArdle disease is relatively stable over time it was anticipated that baseline data from this study and pooled data from previously published studies would be able to provide data for the placebo arm of a future RCT.

3. Results

3.1. Participants demographics

19 participants were screened, and 17 recruited (12 men and 5 women), mean age was 46.2 years (range 21 to 67 years). One recruited participant was withdrawn following screening because he failed to attend a pre-treatment muscle biopsy and V1 assessments (baseline). Two participants failed screening as they did not meet inclusion/exclusion criteria. Two participants dropped out between V1 and V2: one was lost to follow up and the second dropped out because of gastrointestinal AEs. In total, 16 participants attended V1 while 14 participants completed all trial visits.

Mean drug compliance at V3 was 98.7% ± 1.6 (range: 95–100). The mean VPA level at V2 was 72 + −27 (range 29–132) and at V3 66 + −23 (range 28–101).

Table 1

Timepoint	N	Mean ± SD	95% CI for mean	Range
Baseline	16	23.3 ± 6.0		12–33
Baseline#	14	22.9 ± 6.0		12–33
Week 16	12	23.0 ± 4.9		16–30
Week 28	14	22.0 ± 6.4		12–31
Change Baseline to Week 16	12	0.1 ± 3.4	−2.0, 2.3	−5, 7
Change Baseline to Week 28	14	−0.9 ± 5.4	−4.0, 2.2	−13, 5
% Change Baseline to Week 16	12	2.8 ± 16.3	−7.7, 13.2	−21.5, 33.3
% Change Baseline to Week 28	14	−1.7 ± 23.3	−15.2, 11.7	−52.6, 26.3

Summaries of $V0_2$peak (ml/kg/min). # excluding two patients who did not complete the study.

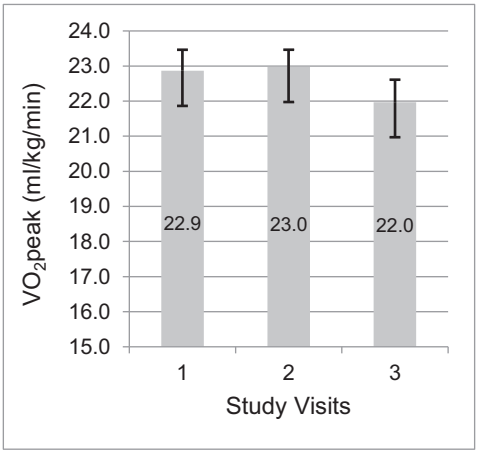

Fig. 1. Mean VO_2peak for participants who completed all trial visits ($n = 14$). Values are mean ± standard deviation. On V2: two participants were not included in mean VO_2peak analysis as they did not perform a maximal test.

Safety blood analyses did not demonstrate any clinically significant alterations.

3.2. Primary outcome

There was no improvement in VO_2peak from baseline to V3 measured by the cycle test (Fig. 1, Table 1).

3.3. Secondary outcomes

Exercise testing: Results for the secondary outcome measures associated with the cycle test are shown in Table 2. There was no clinically meaningful change between baseline and V3.

Muscle biopsy analysis: The median percentage change in the number of phosphorylase positive fibres from baseline and V3 was 0.0 (IQR 0.0, 0.2), while the mean percentage change in the number of neonatal myosin positive fibres was 0.6 + /−2.2 at V3 (SD: ± 2.9) but these fibres did not express phosphorylase.

Forearm exercise test: The mean +/-SD change in plasma lactate from baseline to V3 was 0.12 + /- 0.34 (range −0.52, 0.78) indicating no clinically meaningful difference.

12 min walk test: The mean total distance walked was 966 m (range 683–1292 m) at baseline and 949 m (range 606–1690 m) at V3.The mean variation in the total walked distance was 31 m from baseline to visit 3 was 31 m, indicating a 3% change which does not represent a clinically meaningful difference.

Quality of life: Results for the SF36 Quality of life questionnaire are shown in Table 3. There were no clinically meaningful changes in the two main SF36 health domain scales from baseline to V3.

3.3.1. Adverse events

VPA was tolerated well. None of the participants experienced myoglobinuria during the course of the trial. Table 4 summarises AE data. There were a mean of 10 adverse events per participant (155 in total), most were rated as mild (67%) and unrelated to the study drug (60%). Weight gain was the only definite drug-related AE, the mean weight gain from V1 to V3 was +3.5 kg (SD: 4.8; range: −3 kg to +17 kg) considered to be within the expected range for individuals taking VPA for other reasons. There were 21 AEs (14%) deemed as 'probably' related to VPA. There was one SAE, which was not considered to have been related to the study drug. One participant withdrew from the study due to gastrointestinal symptoms considered to have been related to VPA use.

4. Discussion

This open label study assessed the use of VPA in people affected by McArdle disease. Several endpoints were used to assess treatment efficacy, including the primary endpoint: change in VO_2peak, and secondary endpoints: total distance walked on a 12MWT, forearm exercise test, histochemical expression of phosphorylase enzyme in skeletal muscle and safety blood parameters. There was no clinically meaningful change from baseline to visit three for any of the primary and secondary endpoints.

VPA has previously been shown to stimulate the brain isoform of phosphorylase in two animal models of McArdle disease [17,18]. In the sheep model, animals received increasing doses of enteric administration of enteral VPA (20–60 mg/kg body weight). Muscle biopsies were performed at different times during the treatment phase, and in different muscle groups. In the same study, a group of sheep received intramuscular injections of VPA. An increase in

Table 2

Outcome	Timepoint	N	Mean ± SD	Range
Heart Rate (bpm)	Baseline	16	166 ± 18	135, 197
	Baseline (#)	14	166 ± 18	135, 197
	Week 16	12	168 ± 20	125, 197
	Week 28	14	166 ± 18	132, 190
	Change Baseline to Week 16	12	5 ± 12	−20, 18
	Change Baseline to Week 28	14	0 ± 8	−17, 10
Workload (W) (*)	Baseline	16	49.9 ± 22.9	20, 104
	Baseline (#)	14	45.8 ± 21.4	20, 104
	Week 16	13	44.9 ± 14.3	25, 78
	Week 28	14	46.1 ± 16.7	21, 80
	Change Baseline to Week 16	13	1.0 ± 10.7	−26, 20
	Change Baseline to Week 28	14	0.4 ± 12.5	−26, 20
Glucose (**) (mmol/L)	Baseline	16	4.35 ± 0.47	3.28, 5.33
	Baseline (#)	14	4.48 ± 0.34	4.00, 5.33
	Week 16	13	4.60 ± 0.60	3.83, 6.18
	Week 28	14	4.70 ± 0.62	4.00, 6.50
	Change Baseline to Week 16	13	0.13 ± 0.60	−0.75, 1.65
	Change Baseline to Week 28	14	0.22 ± 0.68	−0.97, 1.98
Lactate (*) (mmol/L)	Baseline	16	0.02 ± 0.40	−0.90, 1.09
	Baseline (#)	14	0.06 ± 0.40	−0.90, 1.09
	Week 16	13	0.12 ± 0.38	−0.23, 1.28
	Week 28	14	0.08 ± 0.49	−0.63, 1.60
	Change Baseline to Week 16	13	0.07 ± 0.27	−0.30, 0.67
	Change Baseline to Week 28	14	0.03 ± 0.38	−0.80, 0.84
Max. Lactate (+) (mmol/L)	Baseline	16	1.06 ± 0.35	0.58, 1.97
	Baseline (#)	14	1.06 ± 0.35	0.58, 1.97
	Week 16	13	1.26 ± 0.38	0.62, 2.18
	Week 28	14	1.27 ± 0.40	0.73, 2.41
	Change Baseline to Week 16	13	0.20 ± 0.21	−0.14, 0.60
	Change Baseline to Week 28	14	0.21 ± 0.23	−0.15, 0.59
Ammonia (**) (μmol/L)	Baseline	16	149 ± 123	50, 532
	Baseline (#)	14	141 ± 130	50, 532
	Week 16	13	158 ± 71	74, 296
	Week 28	14	143 ± 71	53, 312
	Change Baseline to Week 16	13	17 ± 96	−266, 109
	Change Baseline to Week 28	14	3 ± 122	−348, 223

Outcomes related to the cycle test.
(#) Excluding two patients who did not complete the study.
(*) Defined as maximum change from rest.
(**) Defined as mean of post-rest values.
(+) Defined as maximum of post-rest values.

phosphorylase positive fibres was seen in post-treatment muscle biopsies, which increased with higher doses of VPA and over time. However, neonatal myosin staining was not reported to confirm if the phosphorylase activity was related to regenerating fibres or induced. Although neonatal myosin is often used as a marker for fibre regeneration there is evidence it can be up-regulated [20]. Muscle biopsies from a variety of neuromuscular conditions often show fibres with neonatal myosin for unknown reasons [14]. In our study, the presence of a few fibres that showed neonatal myosin but no phosphorylase suggests that these were not regenerating fibres but rather that neonatal myosin had been upregulated. There are currently no antibodies to the brain isoform that reliably work on human muscle biopsies, however, the histochemical stain for phosphorylase detects all three isoforms of phosphorylase, we are therefore confident that VPA treatment did not up-regulate either the brain or liver isoform in our participants.

In the earlier sheep study [17], it was not possible to completely exclude a local toxic effect of intramuscular VPA, which could have triggered muscle regeneration and thus the expression of foetal isozyme in injected muscles. Saline injected sheep showed a few fibres with neonatal myosin suggesting that mild muscle damage may have resulted from injection. In addition, there was a mild inflammatory response, which was not seen in the muscle biopsies of participants in this trial who were treated with oral VPA. However, an *in vitro* study analysed muscle cultures from KI mice exposed to VPA for 72 h at 1, 2 and 5 mM and showed a dose-dependant increase in BGP was shown together with a reduction in intracellular glycogen content [18].

VPA is a well-known drug prescribed as a treatment option for epilepsy and migraine [21]. Its efficacy has also been

Table 3

Outcome	Timepoint	N	Mean ± SD	Range
Mental	Baseline	16	58 ± 5	47, 65
Component	Baseline (#)	14	59 ± 5	47, 65
	Week 16	14	55 ± 7	39, 64
	Week 28	14	57 ± 6	44, 65
	Change Baseline to Week 16	14	−3 ± 4	−7, 1
	Change Baseline to Week 28	14	−1 ± 4	−7, 7
Physical	Baseline	16	43 ± 9	22, 56
Component	Baseline (#)	14	43 ± 9	22, 56
	Week 16	14	46 ± 8	32, 58
	Week 28	14	45 ± 8	30, 54
	Change Baseline to Week 16	14	3 ± 5	−3, 11
	Change Baseline to Week 28	14	3 ± 9	−9, 19
Physical	Baseline	16	52 ± 20	25, 95
Functioning	Baseline (#)	14	49 ± 17	25, 85
	Week 16	14	52 ± 18	27, 90
	Week 28	14	54 ± 15	35, 85
	Change Baseline to Week 16	14	3 ± 8	−6, 25
	Change Baseline to Week 28	14	4 ± 8	−2, 30
Role Physical	Baseline	16	58 ± 21	25, 100
	Baseline (#)	14	54 ± 18	25, 100
	Week 16	14	57 ± 23	25, 100
	Week 28	14	56 ± 23	25, 100
	Change Baseline to Week 16	14	2 ± 17	−19, 56
	Change Baseline to Week 28	14	2 ± 21	−38, 56
Bodily Pain	Baseline	16	50 ± 22	0, 84
	Baseline (#)	14	47 ± 22	0, 84
	Week 16	14	57 ± 25	22, 100
	Week 28	14	54 ± 17	34, 100
	Change Baseline to Week 16	14	10 ± 17	−21, 38
	Change Baseline to Week 28	14	7 ± 20	−21, 62
General Health	Baseline	16	59 ± 15	30, 87
	Baseline (#)	14	61 ± 15	30, 87
	Week 16	14	60 ± 18	15, 87
	Week 28	14	63 ± 17	27, 87
	Change Baseline to Week 16	14	−1 ± 6	−15, 8
	Change Baseline to Week 28	14	2 ± 21	−40, 55
Vitality	Baseline	16	56 ± 12	38, 75
	Baseline (#)	14	55 ± 13	38, 75
	Week 16	14	55 ± 14	31, 81
	Week 28	14	52 ± 16	25, 81
	Change Baseline to Week 16	14	0 ± 15	−15, 18
	Change Baseline to Week 28	14	−3 ± 16	−50, 18
Social	Baseline	16	70 ± 26	13, 100
Functioning	Baseline (#)	14	67 ± 26	13, 100
	Week 16	14	67 ± 24	38, 100
	Week 28	14	66 ± 23	42, 100
	Change Baseline to Week 16	14	0 ± 7	−15, 25
	Change Baseline to Week 28	14	−1 ± 6	−38, 37
Role emotional	Baseline	16	77 ± 23	49, 100
	Baseline (#)	14	74 ± 23	49, 100
	Week 16	14	65 ± 25	46, 100
	Week 28	14	72 ± 22	46, 100
	Change Baseline to Week 16	14	−10 ± 23	−75, 0
	Change Baseline to Week 28	14	−2 ± 7	−25, 0
Mental Health	Baseline	16	67 ± 16	46, 90
	Baseline (#)	14	65 ± 17	46, 90
	Week 16	14	65 ± 15	48, 90
	Week 28	14	68 ± 15	43, 90
	Change Baseline to Week 16	14	0 ± 5	−5, 15
	Change Baseline to Week 28	14	3 ± 7	−5, 20

(#) Excluding two patients who did not complete the study.

Table 4

Outcome	Category	Summary
Adverse events	Total	155
Adverse events per patient	–	10 ± 8 [1, 30]
Adverse events category	Central Nervous System	37 (24%)
	Gastrointestinal	27 (17%)
	Infection	12 (8%)
	Musculoskeletal	44 (29%)
	Other	35 (23%)
Seriousness	Not serious	154 (99%)
	Serious adverse event	1 (1%)
Severity	Mild	102 (67%)
	Moderate	34 (22%)
	Severe	17 (11%)
Relationship to drug	Definitely	1 (1%)
	Probably	21 (14%)
	Possibly	24 (16%)
	Unlikely	19 (12%)
	Not related	89 (58%)

Summary statistics are: Mean ± standard deviation [range], or number (percentage).

evaluated for other conditions, including bipolar disorders and schizophrenia [22,23]. More recently, studies in the field of neuromuscular disease have explored the role of VPA as a histone deacetylase inhibitor (HDAC). Even though *in vitro* studies have indicated an effect of VPA in spinal muscular atrophy, similar efficacy was not confirmed in clinical trials [24,25,26]. A Phase III study of VPA in amyotrophic lateral sclerosis showed no evidence for slowing disease progression or increasing survival [27].

This study showed weight gain and GI disturbances to be the most significant side–effects from VPA, otherwise the drug was well-tolerated, indicating its use would be safe for other indications, such as epilepsy. Migraine and bipolar disorder in the McArdle population. However, this small open label study failed to show any clinically meaningful therapeutic effect.

5. Conclusions

This feasibility study to assess efficacy of 20 mg/kg/day VPA in McArdle disease was planned to power a larger placebo-controlled trial of VPA in this patient population. Our results demonstrated that VPA was well-tolerated but there was no clinically meaningful benefit after 6 months of treatment.

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