RESEARCH ARTICLE

Question-Based Self-Reported Experience of Patients with Subcutaneous Adipose Tissue (SAT) Disease Prescribed Sympathomimetic Amines

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Abstract

Objective: Women with lipedema have painful excess subcutaneous fat on the limbs sparing the trunk. The fat in lipedema has fibrosis making it resistant to loss by diet and exercise (persistent fat). People with Dercum's disease (DD) have painful masses in their fat tissue on the trunk and limbs. Lipedema can be confused with DD. Sympathomimetic amines (SA) such as amphetamine, dextroamphetamine or phentermine anecdotally appear to improve weight loss and quality of life in people with lipedema or DD. The primary objective was to address perceived benefits and downsides of prescribed SA including dextroamphetamine, amphetamine or phentermine in women with lipedema and men and women with DD.

Methods: Fifty-four participants with lipedema and 26 with DD prescribed SA for ≥3 months were consented to respond to a set of 82 categorical scale and descriptive questions and the validated lower extremity functional scale, based on the clinical experience of one of the authors (KLH) and her patients. Significance was set at $\alpha<0.05$. Data were analyzed by Wilcoxon signed rank tests; continuous data was assessed by t-tests.

Results: Participants with lipedema and DD prescribed SA perceived significant improvements in energy level, ability to exercise, leg heaviness, body pain, functionality, and memory. Average self-reported weight decreased by ~25 kg in participants with DD and ~12 kg in women with lipedema consistent with a reduction in clothing size. About 90% of participants felt their quality of life improved. Less than 20% of participants reported side effects from the sympathomimetic amines including insomnia, abdominal pain and visual changes.

Conclusions: People with lipedema and DD report a significant benefit to risk ratio for their fat, pain and quality of life when prescribed sympathomimetic amines. A randomized prospective study would confirm benefits, safety and side effects.

Keywords: appetite, weight loss medication, adipose tissue, obesity, sympathomimetic amines, lipedema, Dercum's disease

1. INTRODUCTION

Lipedema is a fat disease in pre- and post-menopausal women with painful deposits of fat on the limbs much more than the trunk that are resistant to loss by diet and exercise; called *persistent fat*. The prevalence of lipedema is not known but is generally thought to be common. Lipedema fat ranges from slightly increased, tender, grainy to pearl-size nodules, to mounds of thick heavy painful fat classically on the hips, thighs, knees, back and upper arms. Nodules increase in size with stages, and women with Stage 3, over 2 and 1, have more fat tissue increasing the risk of fibrosis, lymphedema and gait impairment. Fat growth and other signs and symptoms of lipedema manifest especially during puberty, but also after childbirth, and at menopause. Joint hyper-flexibility in women with lipedema suggests a change in connective tissue.[1] We and others[2, 3] postulate that an underlying weakness in tissues increases compliance and the ability to hold on to fluids (definition of lipedema). This hypothesis is consistent with loss of elasticity causing lipedema in Williams syndrome.[4] Weaker capillaries may release contents into tissues at a higher rate and/or amount in lipedema which lymphatic vessels promptly pump out. Over time, due to weakness in the fat matrix or lymphatic vessel structure, or due to protein dense and salt-rich[5] deposits in the interstitial space that alter flow through the tissue, lymphatic vessel function reduces or fails, similar to lymphedema. Fluid and nutrients that remain in the interstitial space, a pre-lymph fluid, are postulated to stimulate lipedema fat growth.[6] Hypertrophic adipocytes, a marker of a changed metabolic environment, are reported in lipedema.[7, 8] Strengthening capillary walls, reducing protein and salt deposits in the interstitial space, and improving lymphatic function may improve lipedema.

Dercum's disease (DD) is a rare SAT disease where painful masses are found on the trunk and limbs in more women than men. Fat masses in DD can be pearl-sized in a juxta-articular or global distribution in Diffuse Type as in lipedema, with larger marble, walnut, or golf ball size lipomas or angiolipomas in Nodular Type as in familial multiple lipomatosis, but with pain; Mixed DD combines the two types. Pain is high and pain syndromes are more common in DD than lipedema.[9] Lymphatic disease, metabolic disease including diabetes, and autoimmune diseases have been reported in DD.[11] Many people with DD undergo multiple surgeries to remove the painful fat. Women with lipedema can develop larger fat masses and pain syndromes that result in the diagnosis of lipedema and DD.[9]

Sympathomimetic amines that stimulate the central nervous system causing fat cells to break down stored fat, and act as anorectics, include phentermine, amphetamine, and dextroamphetamine, or a combination of the latter two. [12] Dextroamphetamine improves idiopathic edema (IE), a non-pitting edema in women.[13, 14] A defect in capillaries in IE has been proposed leading to increased leakage of fluid into tissue.[15] Dextroamphetamine has been used to treat IE as it has diuretic properties[16] and side effects are considered minimal due to the low amount of drug (maximal 25 mg oral daily).[17] Effects of SA that may improve lipedema and DD include diuresis reducing tissue salt, lipolysis reducing adipocyte size, vasoconstriction reducing leak, and improved lymphatic function,[18-20] all of which could reduce fat and fat-associated fluid.

Sympathomimetic amines do not improve lymphatic function as well in lymphedema.[21]

People with lipedema and DD have discussed their signs and symptoms in our clinic when SA have been prescribed for attention deficit disorder (ADD), chronic and severe fatigue, narcolepsy, daytime somnolence, and excess sleep, and the benefits anecdotally appear high. This paper describes results of a validated and non-validated questionnaire developed based on experience in our clinic and provided after consent to participants with lipedema or DD to help them report their self-perception of beneficial and adverse effects of SA. The questions focused on four major outcomes: 1) weight loss; 2) signs and symptoms of lymphatic function; 3) quality of life; and 4) adverse events. Secondary outcomes included activity/function, cognition, tissue fibrosis, appetite, and mood.

2. METHODS

Participants were seen in the clinic of a tertiary referral center. Women with lipedema were identified by published criteria[22] with modifications (*italics*): 1. Complaints of pain; 2. Tenderness in the tissue on pressure *and at other times*; 3. Worsening of tissue swelling with orthostasis *and in summer/heat*; 4. *Disproportion between the trunk and the lower body*; 5. *Arms generally affected*. Participants with DD were identified using published criteria:[23] 1. Pain in fat deposits for at least 3 months; 2. Fatigue (asthenia); 3. ≥2 accessory symptoms including cognitive changes, gastrointestinal complaints, joint pain and/or stiffness, muscle pain and/or stiffness and shortness of breath. Participants with lymphedema were diagnosed using a published guideline.[24] Treatments for lipedema, DD and lymphedema include compression garments, sequential pneumatic compression pumps, manual lymphatic drainage (MLD), deep tissue techniques,[25] pain medications, and reduction of non-lipedema fat with diet and exercise; liposuction assisted removal of lipedema fat improves quality of life.[26] Diuretics such as furosemide are avoided to reduce interstitial protein impaction risking progression to lymphedema. Treatment regimens for DD are similar to lipedema but include treatments to prevent cardiovascular disease and diabetes.[27] Patients who presented with diagnoses of attention deficit disorder (ADD), adult attention deficit and hyperactivity disorder (ADHD), daytime somnolence, or excessive fatigue from other providers, or in our clinic by the Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist[25], were treated with SA, being preferred first-choice medications for the short-term treatment of ADHD in adults.[28]

Additional diagnoses for considering SA when other medications had failed (e.g. modafinil, methylphenidate) included severe or chronic fatigue inhibiting activities of daily living, hypersomnia, and narcolepsy. Amphetamine sulfate is approved for the treatment of exogenous obesity (EVEKEO® USP)[29] therefore some patients were prescribed SA for obesity. Symptoms that prevented initiation of SA included atrial fibrillation, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to sympathomimetic amines, glaucoma, known agitation, tachycardia, Raynaud's phenomenon, significant palpitations, severe or chronic migraine or other headaches, debilitating insomnia or history of drug abuse. Side effects of SA were discussed with patients prior to initiation per package instructions, along with discussions of the potential for weight loss.

Patients were evaluated every 3 months for prescription renewal or were followed by their primary care physicians or psychiatrist while on SA and then were seen yearly in clinic. Patients contacted the clinic or other providers with problems or issues with SA which were addressed by phone or clinic visits. Follow up visits included assessments for blood pressure, heart rate, weight, sleep and adverse effects, in addition to fat assessment.

This questionnaire study assessing use of SA was approved by our university's Human Subjects Research Protection Program to consent adult patients with fat disorders if prescribed ≤30 mg dextroamphetamine or equivalent or ≤37.5 mg phentermine for ≥3 months (Figure 1).

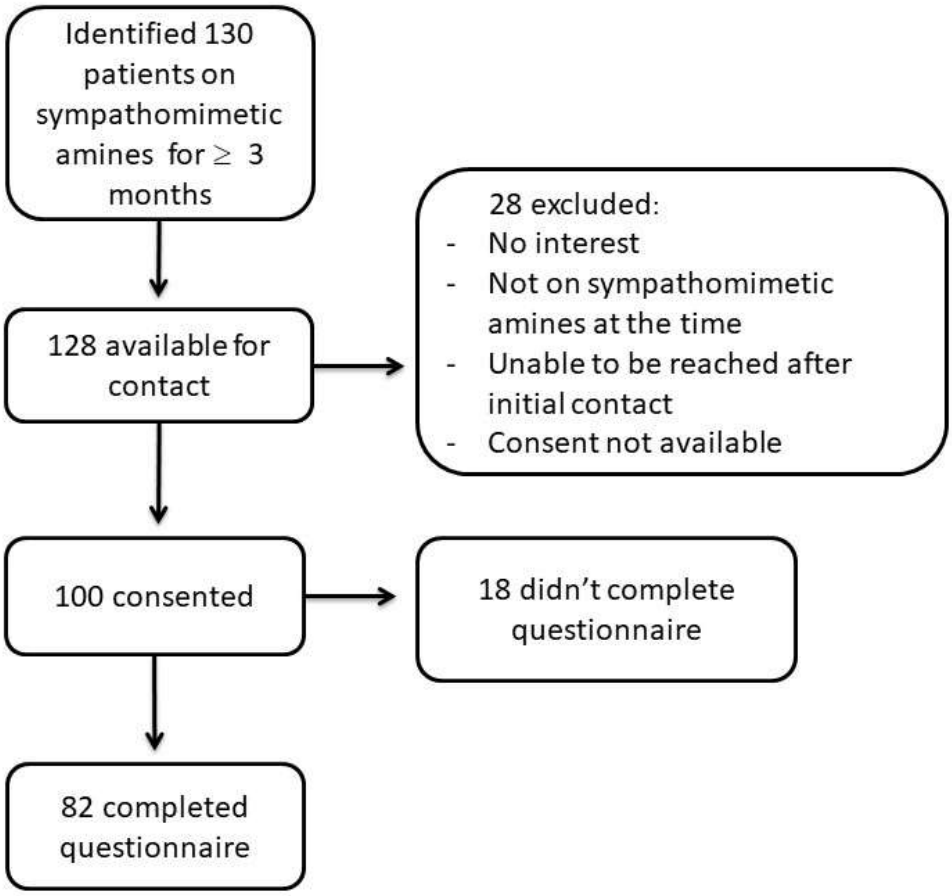

Figure 1: Flow diagram of participants included and excluded from the study.

After consent, participants answered 81 questions collected and managed using REDCap electronic data capture tools hosted at our university[30]. Questionnaire sections (n= number of questions): 1) Demographics, medical and surgical history and current treatments (n=19); 2) SA type and use (n=12); 3) Weight, fat, size, and leg heaviness (n=11);

4) Swelling, edema and shape (n=3); 5) Energy and fatigue (n=4); 5) Exercise, work, activities and function (n=12); 6) Memory and cognition (n=3); 7) Body pain (n=2); 8) Lipomas (n=4); 9) Appetite and food (n=2); 10) Skin and fibrosis (n=4); 11) Manual lymphatic drainage (n=2); 12) Sleep (n=2); and 13) Adverse events (n=1). Adverse event symptoms assessed included migraine headaches, irritability/edginess, mood swings, sleeplessness (insomnia), abdominal (stomach) pain, body pain, palpitations (feeling heart beats), tremors, anxiety, restlessness (includes restless legs), repetitive behaviors, changes in vision (blurry, double, etc.), nausea, addiction and overuse. Activity was assessed by the validated lower extremity functional scale (LEFS) questionnaire.[31] Participants responded to yes or no questions, multiple choice or nominally as a scale. Numerical scales assessed body shape, memory, body pain, fatigue, energy, leg heaviness and function (ability to do things in the participant's daily life compared to normal). Scales corresponded to none (0), average/moderate (50) and highest (100). Appetite scale used was 0=lower, 50=no change and 100=highest.

Data were collected 9/22/16 through 8/24/17. Data were analyzed by Wilcoxon signed rank tests (GraphPad Prism 7, La Jolla, CA, USA) and presented as median (25 and 75 interquartile percentile); a priori α level was 0.05. Continuous data were analyzed by t-test and presented as mean ± standard deviation (SD). Descriptive data are reported as frequencies. Not all questions were answered by all subjects; questions completed (n) are included in the text, figure and tables.

1. RESULTS

3.1 Demographics

Fifty-four participants with lipedema and twenty-six with DD completed the questionnaire (Table 1; Figure 1). Sympathomimetic amines taken by participants included: dextroamphetamine (57%), combination sympathomimetic amines (48%), phentermine (15%), dextroamphetamine extended release (3.6%) and lisdexamfetamine (one participant); 15.8% of participants had tried more than one SA.

Table 1. Participant demographics.

	Lipedema	**Dercum's Disease**
Number of Participants	54	26
Age (years); mean ± SD	52 ± 10.6	48.7 ± 10
Female; number (%)	53 (98)	21 (81)
Weight (kg); mean ± SD	111.3 ± 36.6	95 ± 24.2
BMI (kg/m^2); mean ± SD	40.8 ± 13.4	34.8 ± 9.2
Race; number (%)		
White	50 (93)	24 (92)
African American	4 (7.4)	1 (3.8)
American Indian	1 (1.8)	1 (3.8)
Ethnicity; number (%)		
Hispanic	1 (1.8)	3 (12)
Non-Hispanic	52 (96)	23 (88)
Lipedema; number (%)		
Stage 1	8 (15)	
Stage 2	23 (43)	
Stage 3	22 (41)	
Lipo-lymphedema	12 (22)	
Dercum's Disease Types and Other Diagnoses; number		
Nodular	2	9
Diffuse	7	7
Mixed	8	12
Angiolipomatosis	4	7
Familial Multiple Lipomatosis	2	3
Lymphedema	25	9

Abbreviations: BMI = body mass index; SD = standard deviation.

3.2 Perceived Changes by Participants with Lipedema Before and After Prescribed SA

Lipedema Study Population (n=54): Participants had lipedema mean 19.3 ± 15.5 years; 32% had a concurrent diagnosis of DD (Table 1). Participants with lipedema were prescribed SA for average 2.3 ± 1.7 years; 71% had a diagnosis of ADD, ADHD or chronic fatigue; the remainder had diagnoses including severe fatigue, hypersomnia or narcolepsy. Common medical diagnoses were arthritis and hypothyroidism; hysterectomy was the most common surgery (Table 2). A higher incidence

of diabetes was present in this population compared to previous studies.[1, 9]

Appetite: Appetite decreased for 70.4% of participants, did not change in 22.3% and increased in 7.4%.

Body/Tissue Changes: Participants self-reported significant weight loss after SA (Figure 2) and 77.4% stated their fat improved (n=25). Fat was perceived to be lost from the head (40.7%), neck (40.7%), chest (27%), arms (35%), hands (15%), back (26%), abdomen (52%), buttocks (33.4%), hips (43%), thighs (48%), legs (35%) and feet (22%). Perceived shape improved about average, 50 (36, 69). Participants perceived a significant improvement in leg heaviness, body pain and size (Figure 2). Lipomas were present in 53% of participants; participants felt SA reduced lipoma size in 17.9%, number in 21.4% and lipoma pain in 39.3%. Perceived tissue fibrosis was present in 100% before and 51.3% after SA (n=33).

Cognition and Mood: After SA participants with lipedema had improvements in overall memory (Table 3), short term memory (51.8%), long term memory (35.1%), vocabulary (33.4%), focus (64.8%), word finding (33.4%), name recall (24.1%), productivity (59.3%), creativity (35.2%), anxiety (14.8%), and depression (25.9%).

Activities (LEFS): Participants with lipedema were significantly more active, had more energy, and improved function on SA; fatigue was not significantly different after SA (Table 3). Activities that improved included: any activity (92.3%), standing (42.3%), sitting (30.8%), getting in/out of bed (50%), getting in/out of the tub (26.9%), walking (53.8%), walking long distances (23.1%), exercise (26.9%), running (3.8%), body flexibility (11.5%), and rolling over in bed (30.8%). Seventy-eight percent of participants with lipedema exercised more after taking SA: cycling (12.9%), dancing (7.4%), exercise class (11.1%), gym activity (16.7%), running (3.7%), swimming (35.2%), walking (70.4%), whole body vibration (35.2%), and yoga (24.1%). Days and length of exercise significantly increased (Table 3).

Work: Forty-six percent of participants with lipedema did not work. Of those that worked, improvements with SA included: working instead of becoming disabled (22.2%), working longer (33.4%), working effectively (44.5%), co-workers noticing improved work (5.6%), sociability (31.5%), increased initiative (37%), and self-confidence (37%).

Swelling: Participants noticed decreased swelling after SA in the face (44.5%), neck (31.5%), fingers (35.2%), hands (35.2%), arms (42.6%), chest (25.9%), abdomen (50%), upper back (24.1%), lower back (24.1%), hips (37%), buttocks (31.5%), thighs (57.4%), lower leg (63%), ankles (48.2%), and feet (46.3%). No swelling reduction occurred for 13% of participants.

Side Effects; Overuse of SA: One participant with lipedema twice took extra SA outside the prescribed dose. Symptoms that worsened after SA included: anxiety (7.4%), headaches or migraines (1.8%), insomnia (16.7%), irritability (18.5%), mood swings (7.4%), nausea (3.7%), pain in the abdomen (1.9%) or body (1.9%), palpitations (16.7%), repetitive behaviors (7.4%), restless legs (9.3%), tremors (9.3%), vision changes (11.2%). Forty-one percent of the participants denied any symptoms worsening. There was a small but statistically

significant decrease in self-reported sleep time (Table 3).

Stopping SA: Symptoms that worsened if participants stopped SA included: achiness (17.5%), increased appetite (28%), anxiousness (8.8%), depression (8.8%), diarrhea (1.8%), fatigue (57.9%), functioning normally (19.3%), headaches or migraines (7%), insomnia (1.8%), irritability (15.8%), increased sleep time (29.8%), suicidal thoughts (3.5%), and thinking normally (26.3%). None of the subjects had nightmares, slept better or were happier off SA.

Quality of Life: Less than half (46.3%) of participants struggled to get their prescription filled, due to slow provider response, insurance companies, cost, and pharmacy issues. Just under half (43.4%) were concerned about using SA long-term. Sympathomimetic amines significantly improved quality of life in 94.3% and lipedema in 90.2% of participants.

Table 2. Percentage of participants with medical and surgical histories.

Diagnoses	**Lipedema n=54**	**Dercum's Disease n=26**	**Surgical Procedure**	**Lipedema n=54**	**Dercum's Disease n=26**
Anxiety	29.8	50.5	Breast surgery	29.6	19.2
Arthritis	45.6	42.3	Cholecystectomy	27.7	34.6
Asthma	33.3	30.7	Hysterectomy	35.1	57.6
Cellulitis	21.1	11.5	Lipoma removal	22.2	65.3*
Depression	35.1	57.7	Lymph node resection	3.7	19.2
Diabetes	12.2	23.0	Oophorectomy	24.0	30.7
Pre-diabetes	14	11.6	Pelvic surgery	18.5	15.3
Fibromyalgia	33.3	42.3	Weight reduction surgery	20.3	3.8
Fatty Liver	28.1	34.6			
Hypermobility disorder	29.8	0			
RLS	22.8	23.7			
CAD	1.75	0			
High Cholesterol	26.3	42.3			
Hypertension	26.3	23.0			
Hypothyroid	47.3	34.6			
IBS	36.8	46.1			
MCAS	17.5	19.2			

Abbreviations: CAD= coronary artery disease, IBS= Irritable bowel syndrome, MCAS= Mast cell activation syndrome, RLS= restless leg syndrome. *P=0.0001 vs. lipedema.

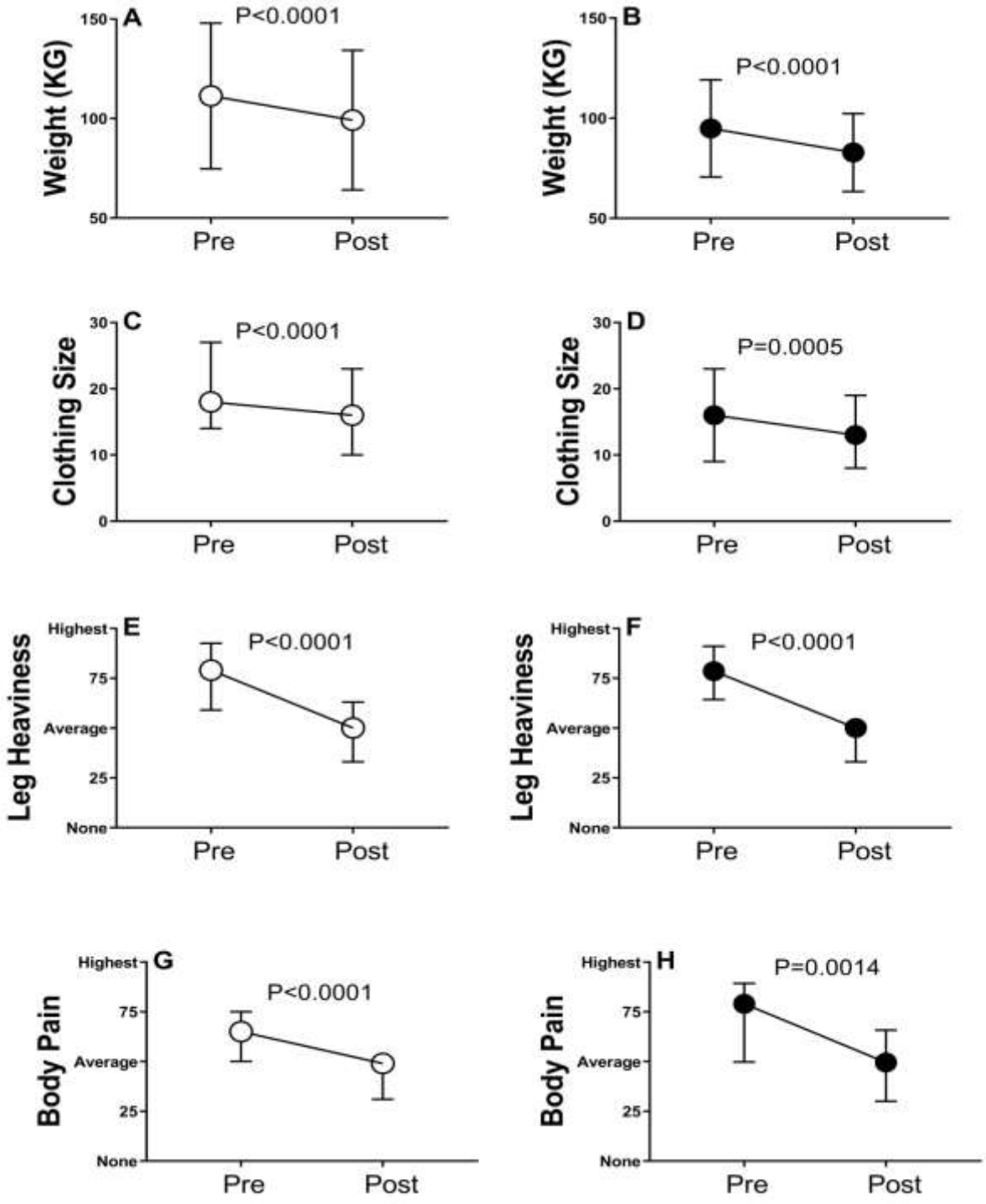

Figure 2: Signs and symptoms improve after sympathomimetic amines for participants with lipedema and Dercum's disease. A, B: Weight; C, D: Clothing Size; E, F: Leg Heaviness; and G, H: Body Pain. Open circles: Lipedema. Closed circles: Dercum's disease. A and B: Data as mean (+/- standard deviation). C, D, E, F, G and H: Data as median (25%, 75% interquartile range). Significant P-values on graphs from Wilcoxon signed rank tests.

3.3 Perceived Changes by Participants with Dercum's Disease Before and After Prescribed SA

Dercum's Disease Study Population (n=26): Participants had DD for 14.7 ± 12 years. None of the participants with DD had lipedema (Table 1). On the questionnaire, 96.1% of the subjects with DD were taking SA for 2.2 (1.2, 3.7) years; 84% had a diagnosis of ADD or chronic fatigue. Over 50% of DD participants had anxiety or depression; the most common surgeries were hysterectomy and lipoma resection (Table 2).

Appetite: Appetite decreased for 84.6% of participants, did not change for 11.5% and increased for 3.8%.

Body/Tissue Changes: Participants lost weight after SA (Figure 2) and scored fat loss as average, 51 (30, 60). Fat was perceived to be lost in the head (57.7%), neck (30.7%), chest (27%), arms (34.6%), hands (12%), back (30.7%), abdomen (61.5%), buttocks (38.5%), hips (34.6%), thighs (38.5%), legs (27%) and feet (19%). Shape improved about average, 51 (35, 65). Participants perceived a significant improvement after SA in leg heaviness, body pain and size (Figure 2). Lipomas were present in 88.5% of participants with DD; SA reduced size in 54%, number in 13% and lipoma pain in 59%. Perceived tissue fibrosis was present in 100% before and 28.6% after (n=14).

Cognition and Mood: Participants with DD had improvements in overall memory (Table 3) short term memory (46.2%), long term memory (38.5%), vocabulary (34.6%), focus (80.8%), word finding (50%), name recall (30.8%), productivity (61.5%), creativity (38.4%), anxiety (34.6%), and depression (42.3%).

Activities (LEFS): Ninety-six percent of participants with DD were more active, had significantly more energy, less fatigue and improved function after SA (Table 3). Activities that improved included: any activity (87%), standing (48%), sitting (25.9%), getting in/out of bed (44.5%), getting in/out of the tub (14.8%), walking (68.5%), walking long distances (29.6%), exercise (42.6%), running (1.9%), body flexibility (35.2%), and rolling over in bed (22.3%). Seventy-six percent of participants with DD exercised more after SA as follows: cycling (11.5%), dancing (3.8%), exercise class (3.8%), gym activity (7.7%), running (3.8%), swimming (23.1%), walking (57.7%), whole body vibration (42.3%), and yoga (7.7%). Days and times of exercise increased significantly after SA (Table 3).

Work: Forty-two percent of participants with DD did not work. Of those that worked, improvements after SA included: working instead of becoming disabled (23%), working longer (30.7%), working effectively (50%), co-workers noticing improved work (15.4%), sociability (23.1%), increased initiative (38.5%), and self-confidence (34.6%).

Swelling: Participants noticed decreased swelling after SA on the face (30.8%), neck (26.9%), fingers (38.5%), hands (30.8%), arms (30.8%), chest (19.2%), abdomen (34.6%), upper back (15.4%), lower back (26.9%), hips (30.8%), buttocks (19.2%), thighs (46.2%), lower leg (46.2%), ankles (38.5%), feet (34.6%). No swelling reduction was appreciated by 15.4% of participants.

Side effects; overuse of SA: None of the participants with DD took SA above that prescribed or felt addicted to SA. Symptoms worsening after SA included: anxiety (3.8%),

headaches or migraines (7.7%), insomnia (19.2%), irritability (3.8%), mood swings (3.8%), nausea (3.8%), pain in the abdomen (15.4%), palpitations (7.7%), repetitive behaviors (3.8%), restless legs (3.8%), tremors (7.7%), vision changes (15.3%). Forty-six percent of participants denied any symptoms worsening. There was no difference in sleep time after SA (Table 3).

Stopping SA: Symptoms that worsened if participants stopped taking SA included: achiness (26.9%), increased appetite (23%), anxiousness (11.5%), depression (15%), diarrhea (3.8%), fatigue (46%), functioning normally (19%), headaches or migraines (11.5%), insomnia (7.7%), irritability (30.7%), increased sleep time (30.7%), suicidal thoughts (3.5%), and thinking normally (38.4%). Off SA 7.6% felt better, 3.6% slept better; none were happier.

Quality of life: Almost half (48%) of participants struggled to get their prescription filled due to problems with the insurance company (50%), but also due to cost (16.7%), pharmacy issues (16.7%), and healthcare providers (16.7%). About 30% stated concern about using SA long-term. Sympathomimetic amines significantly improved quality of life in 88% and Dercum's disease in 91.6% of participants.

Table 3. Signs and symptoms before and after sympathomimetic amines.

Questionnaire Parameter	Participants							
	Lipedema n				Dercum's Disease			
	Before	After	P-value	n	Before	After	P-value	n
Energy Scale*	28 (12, 28)	66 (54, 66)	<0.0001	49	19 (7.8, 31)	56 (40, 80)	<0.0001	22
Fatigue Scale	63 (35, 92)	56 (40, 65)	0.14	47	90 (83, 97)	50 (40, 65)	0.0008	21
Function Scale*	27 (15, 43)	59 (50, 71)	<0.0001	49	26 (18, 35)	57 (43, 75)	<0.0001	24
Memory Scale*	36 (17, 50)	57 (50, 74)	<0.0001	45	25 (12, 41)	60 (50, 67)	<0.0001	25
Exercise (days)	1 (0, 2)	3 (3, 5)	<0.0001	52	0 (0, 2)	3 (2, 5)	<0.0001	25
Exercise Time (hours)	0.25 (0, 0.5)	0.5 (0.5, 1)	<0.0001	52	0.25 (0, 0.75)	0.5 (0.25, 1.25)	<0.0001	24
Sleep (hours)	9 (6, 9.8)	9 (6, 9)	0.0094	53	9 (6, 9.75)	9 (8.25, 9)	0.9	26

*Higher values indicate improvement

2. DISCUSSION

Lipedema and Dercum's disease are painful fat diseases with excessive growth of fat tissue, tissue fluid, and pain that can reduce mobility, result in lymphedema and can be psychologically devastating. This retrospective subjective questionnaire study found that prescribed SA for 53 women and one man with lipedema and 21 women and five men with DD resulted significantly in weight loss, fat loss, and a 3-4 size reduction in clothing as expected by SA known to stimulate adipocyte lipolysis.[32] Indeed, phentermine and amphetamine are FDA-approved weight loss medications. Improvements in lymphatic function known to occur with SA may have been reflected in participant perceived reduction in leg heaviness. As lymphedema

was present in 46.3% of the lipedema and 34.6% of the DD participants, results may be cautiously extrapolated to patients with some forms of lymphedema. It should be noted that standard treatment recommendations were also made for participants at clinic visits and some weight, fat and fluid loss may be secondary to treatments other than SA.

Consistent with weight and fat loss, participants in both groups felt body shape improved significantly, however this improvement was not seen in all participants, reflecting persistence of lipedema and DD fat tissue, and possibly appearance-related distress.[33] A significant increase in activity and exercise and reduction in tissue fluid (heavy legs) consistent with the diuretic action of SA[16] may also have contributed to weight loss.

The cause of pain in lipedema and DD is unknown. Inflammation in the fat tissue may aggravate nerves or increased fluid may apply pressure to the nerves or reduce oxygenation. Sympathomimetic amines significantly decreased whole body and lipoma pain for participants with lipedema and DD suggesting reduction of fluid may be an important factor.

The most striking result from this study was that ≥88% participants had improved quality of life, and >90% had improvement in their fat disorder when taking SA. As lipedema and DD fat cannot be differentiated from non-affected fat, it is unclear whether there was an actual reduction in affected fat but participants did note reduced size and number of lipomas after SA consistent with SA-induced lipolysis.[34] The lipomas seemed to respond better in the DD population but these data require confirmation with quantitative measures. Although subjective, these data are extremely encouraging especially since lipedema fat and DD lipoma fat resist loss by extreme diet, exercise or bariatric surgery (persistent fat).[35]

Individual side effects were reported in less than 20% of all participants. Side effects occurring most often, insomnia in lipedema and DD, palpitations and sleep reduction in lipedema, abdominal pain and visual changes in DD, are known to occur with SA;[36] symptoms appeared to worsen off SA. Of note, blood pressure should be monitored while prescribing SA for patients, and the dose not escalated unless blood pressure is normal or treated. Patients with glaucoma should also be monitored when on SA.

Sympathomimetic amines are most commonly used to help with ADD or hyperactive disorder (ADHD) but have shown benefit in cases of narcolepsy and other disorders of daytime sleepiness,[37] myotonia, fibromyalgia and dysmenorrhea.[38, 39] Sympathomimetic amines may be beneficial in lipedema and Dercum's disease due to improvements in cognition, attention and energy, but also due to improved indicators of swelling such as weight, leg heaviness and shape. That both lipedema and DD have a microangiopathy begs the question of whether the pathophysiology in these disorders is that of IE. In fact, many women with lipedema are thought to have IE.[40]

Normally fluid filtered out of capillaries into the interstitial space is reabsorbed by the lymphatic system.[41] A rise in capillary blood pressure causes increased quantities of fluid to escape. As a result, filtration of fluid into tissues exceeds reabsorption and edema occurs. Arterioles are innervated by adrenergic and cholinergic neurons involved in regulation of

constriction and vasodilation, respectively.[42] Venous pressure increases when standing, causing blood vessels to constrict to maintain blood pressure. In healthy individuals, orthostatic pooling of venous blood in the legs and abdomen begins almost immediately upon the change from supine to the erect posture. One-half to one liter of thoracic blood is transferred to the regions below the diaphragm. Approximately 80% of the blood pooled in the lower limb is contained in the upper leg (thighs, buttocks) with less pooling in the calf and foot; additionally, there is some modest pooling in the abdominal and pelvic regions. When venous filling in the dependent parts raises intravenous pressure to 25 mmHg or more, a local sympathetic 'axon reflex', or 'venoarteriolar reflex (VAR)' is activated. The VAR helps maintain adequate supply of blood to the brain when a person stands. The receptor sites for these reflexes are in small veins in skin, fat, and skeletal muscle tissue and the effector site is the corresponding smooth muscle in arterioles and pre-capillary sphincters. Loss of the VAR has been reported in DD,[43] lipedema,[40] IE, diabetes and with use of nifedipine.[44] Sympathetic input to smooth muscle likely underlies function of the VAR and therefore augmenting sympathetic function with SA may be a viable treatment option for fat disorders.[45] Sympathomimetic amines reduce leakiness of microvascular blood vessels, improve lymphatic pumping,[18-21] reduce liver fat[46] and subcutaneous fat[47] thereby addressing much of the underlying pathophysiology in SAT diseases.

Sympathomimetic amines are not without issues as they have side effects, addiction and dependence risks, are controlled substances and have abuse potential.[48] Two participants (3.7%) with lipedema stated they were addicted to SA, defined as a strong and harmful need to regularly have something. Alternative medications are needed for edema, and could include the stimulant, ephedrine, used to treat IE,[49] or calcium dobesliate for cyclic edema with[50] and without lipedema.[51] Diuretics are generally not used first line in lipedema, lymphedema or DD as they concentrate proteins in the interstitial space which can worsen lymphedema. Anti-inflammatory medications can improve fluid in lymphedema and include sodium selenite[52] and leukotriene B_4 inhibitors.[53] Metformin has also been used to treat cyclic edema.[54]

Subjective data from this study warrants the need for clinical trials testing SA and other medications important in reducing fluid overload in lipedema, Dercum's disease and lymphedema versus placebo to confirm benefit. New research should be funded urgently to assess long-term effects of these drugs, with two FDA-approved SA medications on the market, phentermine and amphetamine sulphate, for weight loss.

Conclusion: People with lipedema and DD report a significant benefit to risk ratio for their fat, pain and quality of life when prescribed sympathomimetic amines. These data add information to the literature on how sympathomimetic amines affect people with SAT diseases. People with SAT diseases may benefit from the mechanism of action of sympathomimetic amines including constricting dilated microvessels reducing leak, improving lymphatic function and increasing lipolysis. Larger prospective studies are warranted to validate benefits and better understand side effects and safety concerns with use of low dose sympathomimetic amines in SAT diseases.

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