Healthcare practitioners' diagnostic and treatment practice patterns of nonalcoholic fatty liver disease in Poland: a cross-sectional survey

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Background Nonalcoholic fatty liver disease (NAFLD) awareness is low. NAFLD diagnosis and management by gastroenterologists (GEs) and general practitioners (GPs) in Poland were evaluated.
Methods RESTORE was an observational, noninterventional, retrospective cross-sectional survey performed among GEs and GPs with at least 3 years' experience. Computer-assisted web interviews were completed. GEs provided information from patient records.
Results Mean experience was 14.2 (95 GEs) and 22.6 (115 GPs) years. Mean patient numbers with liver disorders consulted per month were 36 (13%; GEs) and 51 (6%; GPs); ~50% were patients with NAFLD. All GEs/GPs used ultrasound; most evaluated transaminases and gamma-glutamyl transferase. More GEs used other imaging techniques and a larger spectrum of laboratory tests than GPs. Physician-identified NAFLD key symptoms were similar for GEs/GPs. GEs noticed less obvious symptoms (abdominal discomfort, drowsiness, fatigability, lack of energy) vs. GPs (abdominal pain/discomfort, dyspepsia). Common comorbidities in NAFLD were similar in GE/GP responses. NAFLD interventions by GEs/GPs (% patients) were diet/lifestyle/pharmacological interventions (54%/59%), diet/lifestyle changes alone (41%/31%) or pharmacological interventions alone (5%/10%). The top three criteria for supportive pharmacological selection were efficacy, tolerability and quality of life improvement for GEs/GPs. The five supportive treatments most commonly prescribed by GEs/GPs were essential phospholipids, ursodeoxycholic acid, timonacic, silybinin/silymarin and ornithine + choline. Information from patient records (n = 380) confirmed GEs responses.
Conclusions NAFLD is not a silent disease as physicians and patients reported many, albeit nonspecific, symptoms. This cross-sectional survey provides important insights into clinical management of NAFLD by GEs and GPs in Poland. Eur J Gastroenterol Hepatol 34: 426–434

Introduction

Nonalcoholic fatty liver disease (NAFLD; also known as metabolic-associated fatty liver disease), the most common chronic liver disease is characterized by fat accumulation in the liver without competing etiologies [1]. Worldwide, NAFLD prevalence is ~25% [2,3], being higher in people with certain comorbidities, for example, type 2 diabetes (43–72%) [4], obesity (50–90%) [5] or dyslipidemia (20–80%) [6]. USA predictions suggest that NAFLD prevalence will increase by 21% in 2030 [7].

NAFLD can progress to serious complications, including nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular cancer [8]. Moreover, NAFLD is an independent risk factor for type 2 diabetes [9] and cardiovascular disease [10], and may also be linked to other extrahepatic conditions [11]. Thus, NAFLD is a very significant and increasing healthcare burden.

The mainstay of NAFLD treatment is lifestyle changes including weight loss and physical exercise [2,12,13]; although many patients with NAFLD fail to lose weight [14]. Moreover, NAFLD occurs in people who are lean or nonobese, with a prevalence of 5 and 12%, respectively, in the general population [15]. Thus, in these patients, other NAFLD interventions are needed.

Whilst there are no FDA-approved drugs for NAFLD/NASH treatment, several types of medication are being evaluated – including insulin sensitizers, antioxidants, cholesterol-lowering drugs, modulators of nuclear transcription factors and gastrointestinal hormones [16].

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Other areas of interest are gut microbiota [17], herbal preparations [18] and essential phospholipids [19,20].

Generally, NAFLD awareness is low; for example, in a survey of adults with NAFLD, only 4.4% were aware that they had liver disease [21]. In a survey of hepatologists, gastroenterologists (GEs), endocrinologists and primary care physicians, 47–67% of them considered that very few (<10%) patients with hepatic steatosis have symptoms, although 79–87% acknowledged that patients with NAFLD have impaired quality of life [22]. NAFLD guidelines mostly focus on diagnosis, comorbidities and management options and disease symptoms are outside the focus of current guidelines [2,12,13]; although there is growing evidence that patient-reported outcomes highlight fatigue, abdominal discomfort and sleep disturbance as prevalent symptoms [23,24]. Thus, there is a significant medical need to reduce symptoms in patients with NAFLD.

Treatment recommendations by GEs and general practitioners (GPs) in clinical practice may be different as profiles of patients managed by these two medical specialties might differ. The cross-sectional survey collecting real-world data, RESTORE (**RE**trospective **S**urvey on healthcare provider recommendation of essential phospholipids in NAFLD with focus on most relevant symptoms and their perception regarding efficacy, **T**olerability, **O**nset and needed duration of tr**E**atment), was conducted in Poland. The objectives were to: examine the most relevant tools, symptoms and practices leading to NAFLD diagnosis by GEs and GPs; establish the most common comorbidities in NAFLD; and evaluate which factors contribute to current treatment decisions and hepatoprotectant recommendations and if there are any differences among GEs and GPs.

Methods

Study design

RESTORE was an observational, noninterventional, cross-sectional survey collecting retrospective real-world data from a specific panel of physicians selected for this study, and had two goals: (1) to compare GE and GP practices in diagnosis, assessment and management of NAFLD on the basis of declarations; (2) to reflect actual outpatient practice of GEs in Poland.

There were no additional diagnostic or therapeutic interventions, additional specialist consultations or medical visits. Research was conducted in accordance with the principles of the International Code of Ethics for Market Research ESOMAR and the law in force in Poland (Act on Pharmaceutical Law, Act on Personal Data Protection, Act on the Medical Profession) and compliance with Sanofi's procedures for monitoring and reporting safety information of Essentiale Max, Essentiale Forte and Essentiale Vital.

Physician selection

Eligibility criteria for GEs were: ≥3 years GE work experience; seeing ≥260 patients/month within the practice (open care), or ≥160 patients/month if also working in hospital care. Eligibility criteria for GPs were ≥3 years of GP work experience; seeing ≥400 patients/month within the practice (open care). GEs and GPs also had to know of and use Essentiale (essential phospholipids) for patients with liver steatosis during NAFLD management.

Random-quota sampling was conducted. The sample of physicians were allocated pro rata across territorial layers defined by voivodship ('province' or 'state') and two location types (voivodship cities and others) within Poland. The locations had settings with a contract for primary healthcare or gastroenterology services, on the basis of a contract database published by the National Health Fund. In each layer, 'starting points' were drawn, which were clinics from which physician recruitment started. The number of starting points corresponded to the size of the planned study sample. In the event of a refusal, lack of contact, or selected physicians not meeting eligibility criteria, further physicians were invited from clinics/locations within the same territorial layer as the starting point.

Patient selection

Each recruited GE was asked to select four patients with NAFLD under his/her care. To be eligible, patients had to have seen the GE in open care during the study period and to be diagnosed with NAFLD 1 year prior to the last visit (at the earliest) or during the last visit (at the latest). Patients meeting these criteria were included in the study in the order in which they saw the GE.

Data collection

The GE/GP declarative survey was conducted using computer-assisted web interviews (CAWI). A questionnaire was developed by PEX PharmaSequence (Warsaw, Poland) in cooperation with Sanofi (Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*). GEs were invited during face-to-face meetings, and GPs were invited by phone. The questionnaire was distributed to GEs/GPs via individual links to the PEX platform. The time to complete the questionnaire was ~30 min.

The quantitative survey of patient data was also conducted using CAWI. A second questionnaire developed by PEX PharmaSequence and Sanofi (Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*) was completed online by GEs. Information from the medical records for each patient with NAFLD was used in the questionnaire. All patient data were collected anonymously.

Data analyses

According to Polish National Health Fund reports, there are ~1000 GEs and ~30 000 GPs in Poland (Polish Chamber of Physicians and Dentists). Assuming the sample size requirements for random sampling and maximum response distribution (50%), the sample size for analyses at 80% confidence level with a 6% margin of error was calculated to be 95 GEs and 115 GPs.

All analyses were performed by PEX PharmaSequence using the IBM Statistical Product and Service Solutions package, version 24. As this study described real-world treatment of patients with NAFLD and GE and GP practices, most findings were reported as proportions. The majority of data were reported as categorical variables using percentage distributions. Categorical variables were compared using the Cochran *Q* test or chi-square. Mean and standard deviations were used to describe continuous variables. The Mann–Whitney *U*, Kruskal–Wallis test was

applied to continuous or ordinal variables to assess statistical significance of subgroup differences.

Patient data provided by GEs were subjected to a standard weighting procedure. In the weighting process, the actual number of patients with NAFLD seen by the GE/month (as declared by the GE) was used.

Results

Participating physicians and patient records

Data collection occurred from September 2019 to February 2020. Mean clinical experience for GEs (n = 95) was 14.2 years and 22.6 years for GPs (n = 115). Physicians worked in a variety of institutions with 84% of GEs working in hospital/inpatient care and 97% of GPs were in open care (under contract) (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*). Mean numbers of patients seen by GEs and GPs were 290/month and 785/month, respectively; of these patients, 36.4/month (13%) and 50.8/month (6%), respectively, had liver conditions or diseases. Among patients with liver conditions or diseases, 54% seen by GEs and 49% seen by GPs had NAFLD (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*).

GEs provided information from the medical records of 380 patients with NAFLD (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*). Of these patients, 284 (76%) had further visits to their GEs after NAFLD diagnosis, and 24% (96 patients) were diagnosed with NAFLD at their last visit (Supplementary Fig. 1, Supplemental digital content 1, http://links.lww.com/EJGH/A721). For patients with only one visit at which NAFLD was diagnosed 92% had nonalcoholic fatty liver (NAFL) and 8% had NASH. For patients with at least one subsequent visit after NAFLD diagnosis, 75% had NAFL and 25% had NASH.

Diagnosing nonalcoholic fatty liver disease

Imaging techniques

All GEs/GPs surveyed used abdominal ultrasound as part of the overall assessments to diagnose NAFLD. Transient elastography (liver stiffness and/or controlled attenuation parameter) was performed by 31% of GEs and 11% of GPs ($P < 0.01$; chi-square test). Other imaging techniques used by GEs and GPs, respectively, were: computer tomography (CT) scans (11% vs. 5%) and magnetic resonance imaging (MRI) scans (10% vs. 3%, P = 0.05; chi-square test). A liver biopsy was recommended by 10% of GEs and 5% of GPs.

From the medical records of patients, NAFLD was diagnosed by abdominal ultrasound (98%), elastography (10%), CT (4%), MRI (2%) and/or liver biopsy (3%).

Laboratory tests

Fig. 1 compares laboratory tests used by GEs and GPs for diagnosing NAFLD. Most GEs and GPs tested alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (93% GEs vs. 96% GPs), and gamma-glutamyl transferase (GGT; 87% GEs vs. 78% GPs) levels. Approximately half of GEs and GPs performed alkaline phosphatase (ALP) and bilirubin tests. A lipid profile was used more often by GEs (85%) than GPs (63%; P = 0.05, chi-square test). Blood glucose testing was performed by 67% of GEs and just 30% GPs ($P < 0.01$). GEs analyzed platelets, prothrombin time (internal normalized ratio), and ferritin, total iron-binding capacity and iron more often than GPs.

From patient records, specific laboratory tests performed by GEs in ≥50% of patients were: ALT and AST 95%; lipid profile 72–73%; GGT 70%; glucose 63%; bilirubin 51%; and ALP 50%.

Excluded diseases/disorders

For differential NAFLD diagnosis, both GEs and GPs excluded a wide range of diseases/disorders. Over 97% of physicians excluded significant alcohol consumption. Most excluded chronic hepatitis B or C viral infections (99% GEs, 87% GPs, $P < 0.01$, chi-square test), and significant drug intake (93% GEs, 75% GPs, $P < 0.01$, chi-square test). Other excluded conditions (GEs vs. GPs) were: autoimmune hepatitis (69% vs. 43%, $P < 0.01$, chi-square test); genetic hemochromatosis (61% vs. 31%, $P < 0.01$); improper diet/nutrition (59% vs. 27%, $P < 0.01$); work-related toxicant exposures (48% vs. 43%); Wilson's disease (42% vs. 27%, $P < 0.01$, chi-square test); and other conditions (11% vs. 6%).

From patient records, the most common excluded conditions by their GEs (% patients) were: significant alcohol consumption (99%); significant drug intake (90%); chronic viral hepatitis (88%); and improper diet/nutrition (73%).

Key symptoms leading to nonalcoholic fatty liver disease diagnosis

The symptom most frequently described by physicians using the patient's language was bloating (62% GEs, 57% GPs) (Table 1). From a list of NAFLD symptoms, those observed as occurring 'very often' by GEs vs GPs were abdominal discomfort (43% vs. 43%), abdominal bloating (41% vs. 39%), tired/fatigued (29% vs. 20%), lack of energy (23% vs. 17%) and abdominal pain (19% vs. 20%). More than 60% of GEs and GPs seldom, very seldom or never observed body pain, itching, muscle cramps, joint pain, loss of appetite, difficulty sleeping, problems falling asleep, trouble walking several blocks or climbing the stairs. Some physicians noted that most patients do not report any symptoms (7% of GEs; 4% of GPs).

Compared with GPs, GEs often noticed less obvious symptoms of NAFLD such as abdominal discomfort, drowsiness, fatigability, lack of energy and abnormal tests. GPs were more likely than GEs to notice abdominal pain/discomfort, or dyspepsia symptoms.

Information from patient records on symptoms were consistent with GE declarations (Supplementary Fig. 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*). Most patients (84%) had abdominal symptoms (discomfort, bloating, pain), and 64% had tiredness-related symptoms. Other groups of symptoms were sleep-related (41% of patients), diet/appetite-related (22%) and other symptoms (pain, cramps, itching; 17% of patients). Overall, 11% of patients did not report any symptoms

Profiles of patients with nonalcoholic fatty liver disease

The ratio of men:women with NAFLD seen by GEs was 50%/50%, and by GPs was 54%/46%. The percentage of patients with NAFLD with the most prevalent comorbidities as reported by GEs and GPs, respectively, were abdominal obesity (70% vs. 59%), dyslipidemia (63% vs. 55%), metabolic syndrome (60% vs. 48%), arterial hypertension (55% vs. 41%) and diabetes (46% vs. 39%).

Data patient records provided a comprehensive overview of NAFLD (Table 2). Lifestyle reported by the patients was inactive (83% of patients), diet rich in saturated fats (80%) and smoking (31%). The five most frequent comorbidities were similar to those declared by GEs/GPs. Only 3–4% of patients had a normal weight, 34% were overweight, 42–43% had class I obesity and 17–19% had class II obesity.

Nonalcoholic fatty liver disease treatment

Typical nonalcoholic fatty liver disease interventions

Key NAFLD interventions recommended by GEs/GPs were diet/lifestyle changes and pharmacological interventions (54% and 59% of patients, respectively), diet/lifestyle changes only (41% and 31% of patients, $P = 0.05$, Mann–Whitney *U* test), or pharmacological interventions only (5% and 10% of patients, $P = 0.05$, Mann–Whitney *U* test) (Fig. 2). For drug treatment, monotherapy was recommended to approximately two-thirds of patients by both GEs and GPs, and polytherapy to approximately one-third of patients. GEs and GPs noted that 48% and 44%, respectively, of their patients were independently using over-the-counter medications for NAFLD.

From patient records, types of treatment recommended directly after NAFLD diagnosis by GEs were diet-related/lifestyle changes for 99.5% of patients and drug treatment (including herbal preparations) for 79.9% of patients. Of the 302 patients advised to take pharmacological interventions (including herbal preparations), 48%, 32%, 15%, 4%, 0.5% and 0.5% were recommend 1, 2, 3, 4, 5 and 6 pharmacological interventions, respectively. For polytherapy, GEs recommended a range of products for 24% of these patients (for the patient to choose from) and 76% of these patients were advised to use all of the pharmacological interventions recommended.

Criteria for pharmacological interventions choice

Regarding choice of pharmacological interventions, GEs and GPs were asked to rank seven criteria using a scale of 1 (not relevant at all) to 5 (extremely relevant). The top three criteria for drug choice for both GEs and GPs were efficacy, tolerability and improvement of quality of life (Table 3).

Key supportive pharmacological interventions

Each physician listed five pharmacological interventions they prescribed most often, regardless of use as monotherapy or in polytherapy (Fig. 3). Most GEs (92%) and GPs (98%) recommended essential phospholipids (study inclusion criterion). Other pharmacological interventions frequently recommended were ursodeoxycholic acid, timonacic, silybinin/silymarin, and ornithine + choline (Fig. 3). As NAFLD is a chronic disease, 59% of GEs and 62% of GPs recommended long-term pharmacological treatment.

For the top three criteria impacting drug choice, those ranked highest for efficacy were Essentiale (GEs) and Heparegen (GPs). GEs/GPs ranked Essentiale the highest for tolerability. For improvement of quality of life, Essentiale and Heparegen were ranked equally by GEs/GPs (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*; Supplementary Fig. 3, Supplemental digital content 1, *http://links.lww.com/EJGH/A721*).

From patient records ($n = 302$), the four most frequently recommended therapies (% patients) were: essential phospholipids (17%), timonacic (8%), silybinin/silymarin (6%), and ursodeoxycholic acid (5%). The symptom 'lack of energy' was relieved in 79% of patients with essential phospholipid treatment compared with 51% of patients receiving timonacic ($P = 0.05$, chi-square test).

Tolerability of selected pharmacological interventions

Regarding drug tolerability, GEs and GPs were asked to rank the tolerability of the five commonly recommended pharmacological interventions using a scale of 1 (not tolerated at all) to 5 (extremely well tolerated). For the top five pharmacological interventions recommended, Table 4 shows the tolerability ranking. Essentiale (essential phospholipids) was ranked as very well tolerated by GEs and GPs.

Discussion

This survey of GEs and GPs in Poland provided key information on NAFLD diagnosis, typical comorbidities in NAFLD, as well as factors contributing to treatment decisions, including hepatoprotectant recommendations.

For NAFLD diagnosis, all GEs and GPs used abdominal ultrasound. Other imaging techniques were used much less frequently by GEs/GPs, although more GEs used elastography, CT scan, MRI scan and liver biopsy vs. GPs. These differences are expected given current medical practice in Poland. GPs do not refer patients for scans or biopsies and do not interpret findings from tests conducted by specialists. Thus, GEs are more likely to diagnose NAFLD having more experience and greater access to other services vs. GPs. Abdominal ultrasound for NAFLD diagnosis is recommended in guidelines as a first approach due to wide availability, low cost, no safety risks [2,12,13], and is considered an adequate imaging technique to aid GPs in Poland in diagnosing NAFLD. Indeed, a meta-analysis of ultrasonography vs. histology reported that the sensitivity and specificity of ultrasound were 85% and 94%, respectively, for detecting moderate-to-severe fatty liver [25].

Most physicians participating in this study tested ALT, AST and GGT levels, and approximately 50% evaluated alkaline phosphatase and bilirubin levels. However, significantly more GEs evaluated lipid profiles and glucose levels than GPs. Interestingly, the range of laboratory evaluations conducted by GEs/GPs exceeded basic tests recommended in NAFLD guidelines [2,12,13].

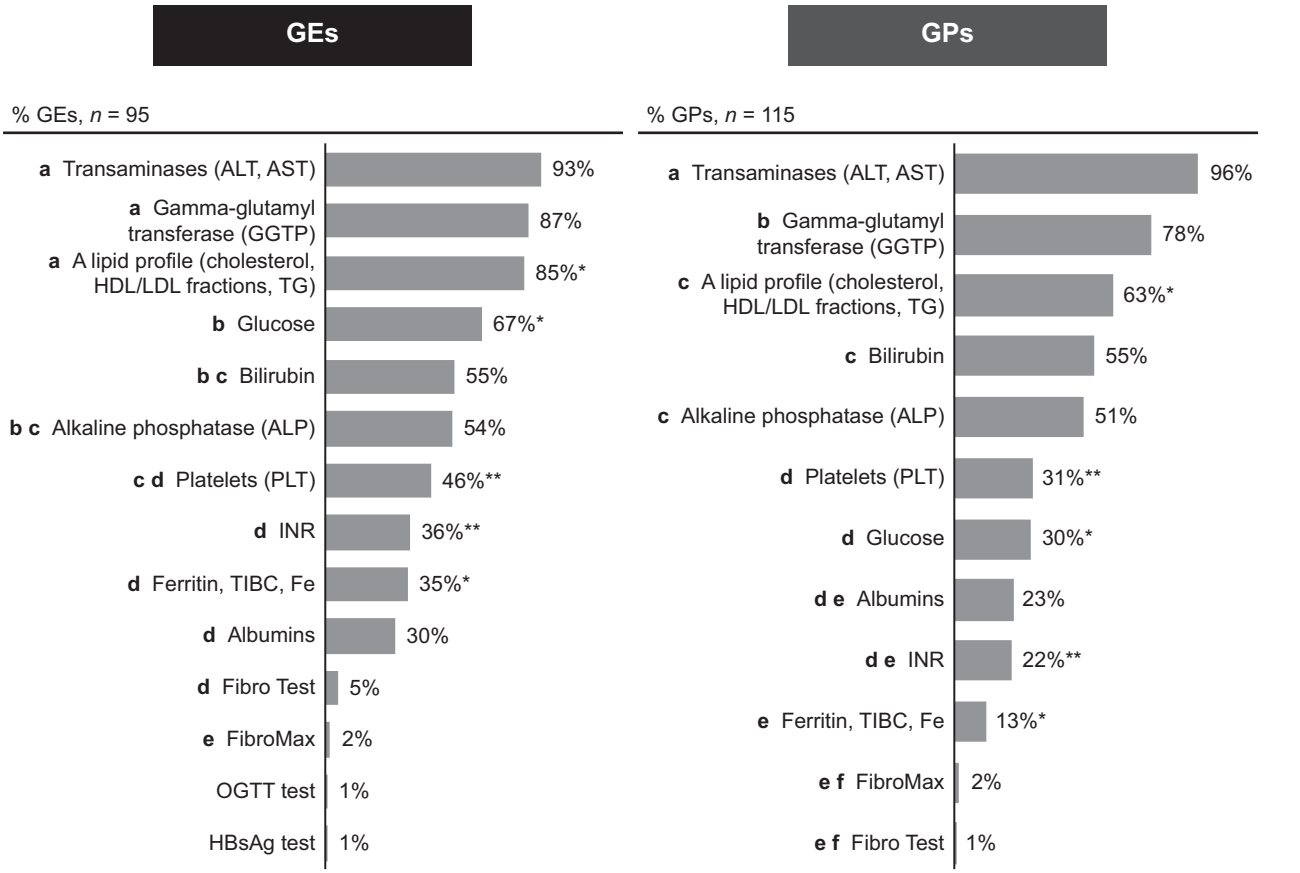

Fig. 1. Laboratory tests used by GEs and GPs to diagnose NAFLD. Differences between use of laboratory tests within each group (i.e. within GEs and within GPs) are marked with letters. If the same letter is shown, there is no difference between the proportion of GEs (or between the proportion of GPs) using those laboratory tests. If the letters are different, the proportion of GEs (or the proportion of GPs) using those laboratory tests is statistically significantly different, $P = 0.05$ (Cochran Q test). For each laboratory test, statistically significant differences between GEs and GPs are shown by $^{*}P < 0.01$, $^{**}P = 0.05$ (chi-square test). ALP, alkaline phosphatase; ALT, alanine aminotransferase; Fe, iron; GEs, gastroenterologists; GGTP, gamma-glutamyl transferase; GPs, general practitioners; HDL, high-density lipoproteins; INR, international normalized ratio (prothrombin time); LDL, low-density lipoproteins; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; PLT, platelets; TG, triglycerides; TIBC, total iron-binding capacity.

Table 1. Top five most common symptoms of NAFLD reported by GEs and GPs using patients' language

GEs $N = 95$		GPs $N = 115$	
Symptom	% GEs	Symptom	% GPs
Bloating	62	Bloating	57
Weakening	33	Pain[a]	47
Tiredness/fatigue	31	Weakening	21
Pain[a]	28	A feeling of fullness	27
A feeling of fullness	24	Stomach aches	26

GEs, gastroenterologists; GPs, general practitioners; NAFLD, nonalcoholic fatty liver disease.
[a]Right upper quadrant pain/below right ribs/in the right side/in liver area, $P < 0.01$ (Mann–Whitney U test).

NAFLD diagnosis as the primary disease requires exclusion of certain factors and coexisting conditions which impact hepatic steatosis [2,12,13]. In RESTORE, most GEs/GPs excluded patients with significant alcohol consumption and those with chronic hepatitis B or C. However, more GEs vs. GPs also excluded patients with other conditions. GEs/GPs did follow recommendations for excluding patients from a primary NAFLD diagnosis, but GEs were more aware of exclusion conditions, possibly due to their greater experience in liver diseases.

This cross-sectional survey collecting real-world data in Poland provided an ideal opportunity to describe symptoms experienced by patients with NAFLD. This topic is important given that the majority of physicians consider NAFLD to be an asymptomatic disease [22], and guidelines do not mention symptoms as part of the diagnosis pathway [2,12,13]. RESTORE demonstrated that only a few patients with NAFLD had no symptoms; 7% of GEs and 4% of GPs had some patients with no symptoms, and 11% of patients from GE records were asymptomatic. GEs/GPs noted the five most common symptoms/problems as described by patients (bloating, weakening, tiredness/fatigue, epigastric pain, feeling of fullness and stomach pains) and also rated the frequency of symptoms from a list (symptoms occurring very often were: abdominal discomfort, abdominal bloating, tired/fatigue, lack of energy and abdominal pain). Interestingly, there was a tendency for GEs to consider more general/less specific symptoms (fatigue, loss of energy) in relation to NAFLD diagnosis, compared with GPs. This observation is in keeping with patient-reported outcome studies highlighting fatigue, abdominal discomfort and sleep disturbances as prevalent NAFLD symptoms [23,24]. Thus, RESTORE highlights NAFLD as a symptom-burdened disease, which is not surprising as NAFLD is a clinically heterogeneous syndrome with disproportionate contribution of metabolic, genetic

Table 2. Patient characteristics from patient records held by GEs

Parameter	Patients *N* = 380	
	Men	Women
n (%)	201 (53)	179 (47)
Age, years		
Mean	51	55
Median (range)	51 (21–74)	56 (29–87)
	All patients	
Age range, %		
≤35 years	7%	
36–45 years	20%	
46–55 years	28%	
56–65 years	34%	
>65 years	11%	
BMI, kg/m^2, mean (median [range])[a]		
At time of diagnosis (*n* = 96)[a]	31 (31 [23–50])	
At last visit (*n* = 284)[b]	32 (31 [20–60])	
Five most common comorbidities (% patients)		
Abdominal obesity	85%	
Dyslipidemia	75%	
Arterial hypertension	69%	
Metabolic syndrome	56%	
Diabetes	30%	
No. of 5 most common comorbidities (% patients)		
5	19%	
4	31%	
3	16%	
2	18%	
1	12%	
Comorbidities other than top 5	1%	
No comorbidities	3%	

BMI, body mass index; GEs, gastroenterologists.
[a]Patients who had only one visit at which NAFLD was diagnosed.
[b]Patients who had at least one subsequent visit after NAFLD diagnosis.

and environmental factors [26]. The present findings demonstrate that many symptoms, albeit general/nonspecific, should play a greater role, than at present, in NAFLD diagnosis. Awareness needs to be raised by different societies and in guidelines about the wide range of nonspecific NAFLD symptoms, particularly as some symptoms could be suggestive of functional gastrointestinal disease [27]. Recently, a European NAFLD registry has been set up, which includes evaluating symptom burden [28].

Overall, RESTORE confirmed that the characteristics of patients with comorbid metabolic diseases closely correspond with known profiles of patients with NAFLD. Though it has been suggested that males may be at greater risk of NAFLD than females [2,3], the ratio of men to women in RESTORE was ~50:50. Older age is another risk factor in NAFLD [2,3,13]. Mean age of patients in RESTORE was 51 (men) and 55 (women) years, and approximately one-third of patients were aged 56–65 years. From the GE/GP survey, the most prevalent comorbidities associated with NAFLD matched reported risk factors for this disease (abdominal obesity, dyslipidemia, metabolic syndrome, arterial hypertension and diabetes) [2–6,13]. In RESTORE, 3–4% of patients with NAFLD were of normal weight, in keeping with a NAFLD prevalence of 5% in lean people in the general population [15]. From the records of patients with NAFLD, 97% of patients had concomitant diseases and many had multiple comorbidities. These records noted some patients had NASH, however, this diagnosis was made on the basis of laboratory parameters, whereas NASH should be diagnosed through histopathology [2,12,13].

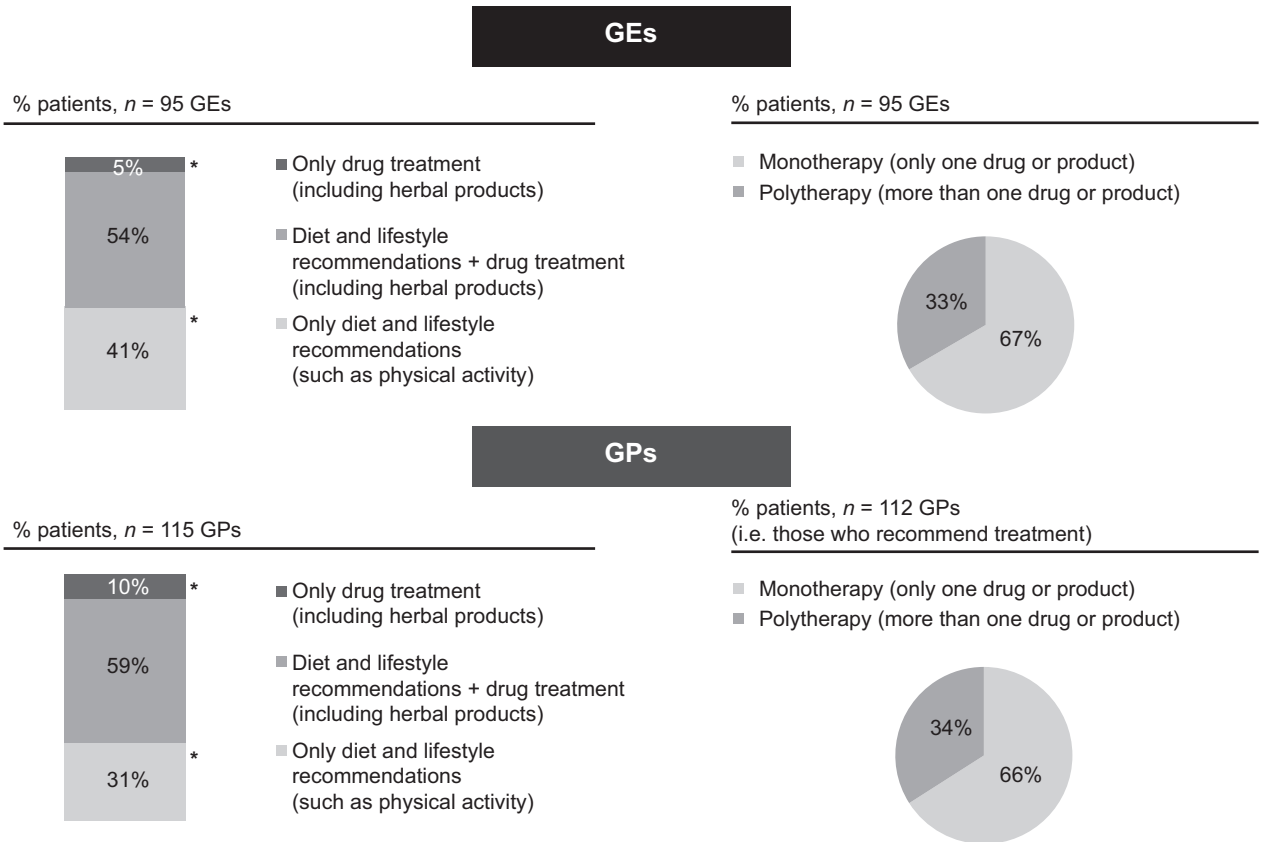

Fig. 2. Drug treatment or recommendations for patients with NAFLD. The differences between GEs and GPs are significant ($P = 0.05$) are marked with *, Mann–Whitney *U* test. GEs, gastroenterologists; GPs, general practitioners; NAFLD, nonalcoholic fatty liver disease.

Most patients in RESTORE were recommended diet/lifestyle changes, alone or in addition to pharmacological interventions for NAFLD management. Efficacy, tolerability and improvement of quality of life were the most important criteria for drug selection by GEs and GPs. This observation puts patient-reported outcomes as an important reason for choosing hepatoprotectants as part of NAFLD management, which is particularly encouraging in recognition of the impact of NAFLD on quality of life [23,24].

For GEs/GPs, the most frequently recommended therapeutic interventions other than essential phospholipids were a food supplement of ornithine and choline, and the medicinal products silybinin/silymarin, ursodeoxycholic acid, and timonacic. This finding emphasises the common use of hepatoprotectants in Poland, with no major differences between GEs and GPs in recommending them.

The most evidence for a hepatoprotective effect is available for essential phospholipids. In patients with NAFLD only, NAFLD and diabetes, or NAFLD and mixed hyperlipidemia, essential phospholipids with a diet/exercise plan significantly reduced ALT and AST levels, improved symptoms, and improved liver ultrasound scans and liver stiffness [29,30]. Evaluations of clinical studies noted that essential phospholipids in fatty liver disease improved/normalized sonographic features of steatosis [30,31]. Essential phospholipids, as an adjuvant to diet, effectively decreased hepatic steatosis and insulin resistance in overweight patients with NAFLD and hypertension [30,32].

A real-world evidence study in Russia demonstrated improved sonographic features of NAFLD with essential phospholipids treatment of patients with at least one of four comorbidities (overweight/obesity, hypertension, diabetes, hypercholesterolemia) [20]. There are no published evidence on ornithine/choline hepatoprotective effects. However, data with L-ornithine/L-aspartate given orally for 12 weeks at 6–9 g/day showed a dose-related reduction in liver enzyme activity, triglycerides and improvements in liver:spleen CT ratios in patients with fatty liver of diverse etiology [33]. Silybinin/silymarin has shown hepatoprotective effects in patients with NAFLD, e.g. reduced liver-related deaths, improvement of glycaemic parameters, and treatment of drug-induced liver injuries

Table 3. Ranking of criteria for choosing pharmacological interventions for NAFLD treatment

Criterion	Mean ranking score[a] GEs *N* = 95	GPs *N* = 115
Efficacy	4.7	4.6
Tolerability	4.4	4.3
Improvement of quality of life	4.4	4.3
Own experience with product	4.3	4.2
Cost of therapy	3.7	3.7
Duration of treatment	3.5	3.5
Fast onset of action	3.5	3.5

GEs, gastroenterologists; GPs, general practitioners; NAFLD, nonalcoholic fatty liver disease.
[a]Physicians ranked each criterion using a scale of 1 (not relevant at all) to 5 (extremely relevant).

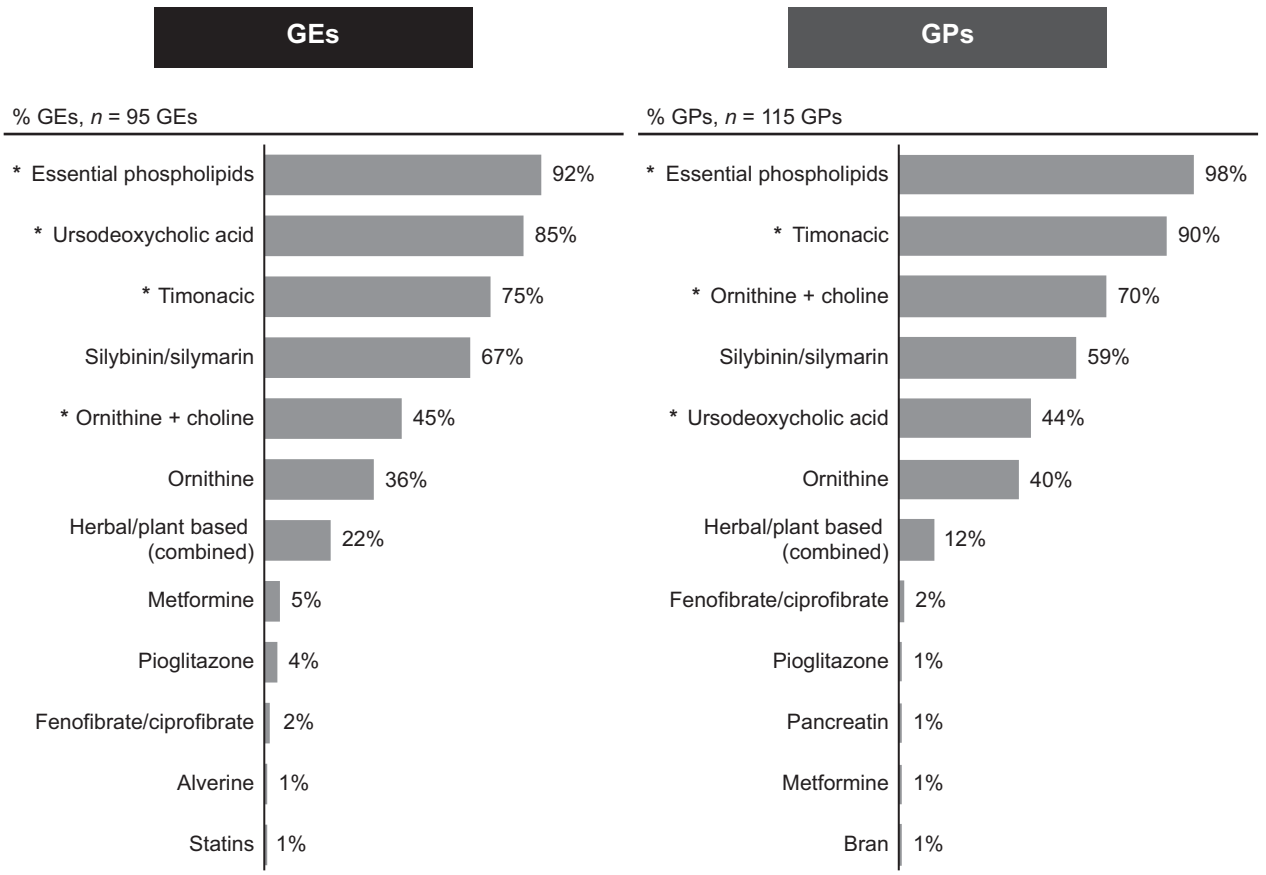

Fig. 3. Most frequently prescribed drug treatments for NAFLD by GEs and GPs. *The differences between GEs and GPs are significant at $P = 0.05$ (chi-square test). GEs, gastroenterologists; GPs, general practitioners; NAFLD, nonalcoholic fatty liver disease.

Table 4 GE and GP ranking of tolerability of the top five pharmacological interventions prescribed for NAFLD

	Mean ranking score[a]	
Treatment	GEs *N* = 95	GPs *N* = 115
Essentiale	4.5	4.6
Sylimarol	4.4	4.4
Heparegen	4.4	4.3
Hepatil	4.3	4.2
Proursan[b]	4.1	3.6

Essentiale (essential phospholipids); Hepatil (ornithine + choline); Heparegen (timonacic); Proursan (ursodeoxycholic acid); Sylimarol (silybinin/silymarin).
GEs, gastroenterologists; GPs, general practitioners; NAFLD, nonalcoholic fatty liver disease.
[a]Physicians ranked each treatment using a scale of 1 (not tolerated at all) to 5 (extremely well tolerated).
[b]$P < 0.01$ (Mann–Whitney U test) for GEs vs. GPs.

[34]. Ursodeoxycholic acid is approved for primary biliary cholangitis [35] and has been shown to improve fatigue in patients with abnormal liver function tests, or NAFLD [36]. Finally, timonacic has been used for many years as an hepatoprotectant, although it is only available in Poland and Egypt. This compound is generally considered to be an effective antioxidant drug, although there is very limited information to confirm this assumption [37].

There are no FDA-approved pharmacological interventions for NAFLD/NASH, although several medication types are being evaluated [16]. Although herbal preparations [18] and essential phospholipids [19] are of interest in NAFLD management, such hepatoprotectants are rarely included in guidelines [2,12,13]. The antioxidant, vitamin E, is recommend in Latin American [12] and American [2] guidelines but not in Europe [13]. Two of these guidelines advise against the use of ursodeoxycholic acid [2,13]. Russian [38] and Chinese [39] NAFLD guidelines recommend essential phospholipids. Silybinin/silymarin is recommended in Chinese guidelines [39]. Thus, there is no consensus on hepatoprotectants in NAFLD management. Given that the surveyed GEs/GPs from Poland in RESTORE recommended hepatoprotectants, they may be guided more by advertising information than by scientific literature and recommendations of scientific societies.

Findings from the GEs in the qualitative part of RESTORE were fully supported by the quantitative data from patient records, which validates the qualitative survey. Practice patterns for NAFLD have also been reported in other countries, e.g. Romania [40], France [41] and Germany [42]. While there are many similarities between RESTORE and other published surveys, a common factor is the use of non-approved/non-recommended hepatoprotectants.

RESTORE has certain limitations. One of the inclusion criteria for GEs/GPs was recommendation of essential phospholipids (specifically Essentiale). As only 4% of the 238 GPs screened for the study did not meet this criterion, this inclusion requirement did not have a significant impact on the population of surveyed physicians. Only 11% of patients (GE records) were >65 years old; although age was not a selection criterion in this study. Thus, this age group was potentially under-represented as the prevalence of NAFLD is high in older people, for example, 40% in people aged 60–74 [43] or 51% in those aged 65–70 years living in Poland [44].

In conclusion, RESTORE demonstrated that NAFLD is not a silent disease; rather, both GEs/GPs and patients report many, albeit nonspecific, symptoms. This cross-sectional survey provides important insights into clinical management of NAFLD by GEs and GPs in Poland.

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Qualified researchers may request access to patient-level data and related study documents including the study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data are anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.

Conflicts of interest

M.H. has received honoraria for sponsored lectures from Sanofi and Promed. A.M.-M. has received honoraria for sponsored lectures from Sanofi, Promed and Bausch. P.K. has received an honorarium for a study sponsored by Sanofi. B.O. has received honoraria for sponsored lectures from Sanofi. B.P. is an employee of Sanofi Aventis Deutschland and may hold shares and/or stock options in the company. K.P. is an employee of PEX Pharma Sequence. B.C.-D. is an employee of Sanofi-Aventis Sp. z o.o and may hold shares and/or stock options in the company.

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