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National Pharmacy and Therapeutics Committee
Non-Alcoholic Fatty Liver Disease
NPTC Formulary Brief
February Meeting 2017

Background:
Non-alcoholic fatty liver disease (NAFLD) is a group of diseases classified by adipocyte infiltration of the liver in the absence of alcohol consumption, viral hepatitis, medication or toxic damage or autoimmune hepatitis[1]. NAFLD is broken up into several disease states characterized by the histology of each. In nonalcoholic fatty liver or non-alcoholic steatosis, triglyceride-containing vacuoles are deposited in and around hepatocytes without inflammation. Non-alcoholic steatohepatitis (NASH) is characterized by steatosis plus inflammation. Non-alcoholic cirrhosis is steatohepatitis that has progressed to fibrosis, leading to hepatic failure and increased risk of developing hepatocellular carcinoma (HCC)[1]. It is currently estimated that 19-46% of the general US population has NAFLD[1-3] and 3-5% with NASH[2]. NAFLD is thought to be the most common cause of chronic liver disease in the Western hemisphere and that by 2020 will be the most common cause of end stage liver disease[5]. Risk factors for NAFLD include dyslipidemia, obesity, and insulin resistance, all components of the metabolic syndrome. Patients with type 2 diabetes mellitus (T2DM) have a 2-fold increase in risk of developing NASH and non-alcoholic cirrhosis[4]. It is estimated that the prevalence of NAFLD in the American Indian and Alaskan-Native (AI/AN) populations ranges from 0.6-2.2% but this is thought to be an underestimate[2]. In a study from 2010, the risk of death from chronic liver disease in AI/AN was 35.4 percentage points higher than whites from the same region[7]. Given both the prevalence of risk factors for NAFLD among AI/AN (24-40% for obesity, 9.7-19.7% for T2DM) and higher rates of death from chronic liver disease in this population, potential treatments for this disease are of particular interest to the Indian Health Service (IHS) National Pharmacy & Therapeutics Committee (NPTC). Following the NPTC clinical evaluation in February 2017, no changes were made to the IHS National Core Formulary.

Discussion:
The goals of treatment of NAFLD are to reduce hepatic fatty infiltration, reduce inflammation, and reverse fibrosis. The most effective non-pharmacologic therapies for NAFLD are lifestyle modifications leading to weight loss. Weight loss of 3-5% of body weight is necessary to improve steatosis and up to 10% weight loss is necessary to improve inflammation associated with NASH[2]. There are currently no FDA-approved medications for the treatment of NAFLD or NASH, however two pharmacologic therapies are recommended by the American Gastroenterological Association (AGA) and several others are in clinical trials to address both NAFLD and NASH[2]. The current AGA recommended therapies are vitamin E and pioglitazone for the treatment of NAFLD.

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Findings:
Vitamin E is a fat soluble vitamin available over the counter. The proposed mechanism of action of vitamin E in NAFLD is reduction of oxidative stress preventing inflammation and progression to fibrosis[8]. The most commonly used dose is 400-800 IU/day. Vitamin E is classified as a dietary supplement thus all uses are considered off-label. Notably, two meta-analyses reported increased all-cause mortality with high-dose vitamin E however subsequent and more recent studies failed to confirm the association[2]. Pioglitazone is recommended by the AGA as a second line agent to treat "biopsy-proven NASH" and should be used with caution in T2DM patients as clinical trials that investigated the drug were conducted in non-diabetic patients.

Pioglitazone is a thiazolidinedione whose mechanism of action in NAFLD is thought to be two-fold: reduction of hepatic fatty acids via PPA-gamma receptor activation and prevention of inflammation, necrosis and fibrosis by decreasing levels of adipokines[2,9]. Notable warnings for pioglitazone include a black box warning for CHF causation or exacerbation, increased risk of bladder cancer (Hazard ratio=1.63), edema, increased incidence of long-bone fractures and dose-related weight gain[9-10]. Pioglitazone alone has been studied in several randomized controlled trials (RCT). Three trials from 2008-2016 with both diabetic and non-diabetic patients had significant improvements in histology associated with NASH[11-13]. In fact, a small RCT of pre-diabetic and diabetic patients demonstrated a significant improvement in the primary outcome of >2-point reduction in steatosis score without worsening of fibrosis (36 percentage points; P<0.001). All three studies failed to show reversal of fibrosis[11-13].

In 2010, Sanyal et al. published the results of a RCT of 247 non-diabetic patients which continues to be the most compelling evidence for vitamin E and pioglitazone in the treatment of NAFLD. Patients were randomized to 3 arms (vitamin E 800 IU daily, pioglitazone 30mg daily, and placebo) for 96 weeks. Patients with CHF, cirrhosis, Hep C or other liver disease were excluded. These patients had a pre-treatment and post-treatment biopsies and the degrees of steatohepatitis was assessed using a score of steatosis, lobular inflammation and hepatocellular ballooning (HCB). Primary outcome was improvement in HCB of 1 point, no increase in fibrosis and at least 1-point improvement in steatosis or lobular inflammation. Outcomes were notable for vitamin E superiority to placebo in the primary outcome (43% vs. 19%, P=0.001; number needed to treat = 4.2). Pioglitazone trended towards improvement but was not significant (34% vs. 19%, P=0.04; number needed to treat, 6.9). Neither therapy showed improvement in fibrosis. This study was limited by the subjectivity of histologic analysis and was not designed to compare vitamin E versus pioglitazone. Adverse events were similar in all arms.

As mentioned above, pioglitazone is recommended with reservation by the AGA. Vitamin E is considered first line therapy for biopsy-proven NASH in non-diabetic patients (1B recommendation) but not recommended for use in patients with T2DM with NASH, NAFLD without biopsy, or in NASH cirrhosis. European guidelines make similar recommendations and no Cochrane Reviews exist discussing these two therapies[15-16].

There are a number of therapies that have been reviewed by the Cochrane database with regards to treatment for NAFLD. Bariatric surgery was reviewed and found to have no randomized or quasi-randomized trials fulfilling criteria and no conclusion could be reached[17]. Similarly, for weight reduction, 5 trials existed, two examining orlistat in NAFLD, however data was too sparse for meta-analysis[19]. The most compelling Cochrane data exists for statin use in NAFLD. Two RCTs were reviewed (one comparing simvastatin to placebo and the other comparing fenofibrate, atorvastatin and placebo). The conclusions were that neither trial had assessed histologic changes or liver-related morbidity and mortality and both were small. No conclusions could be drawn that statins were an effective treatment for NASH, however authors did suggest that the use of statins in NASH is justified given the high rate of comorbidities of dyslipidemia, diabetes and metabolic syndrome.

The use of statins in NAFLD is widely supported by gastroenterological societies worldwide[2, 15-16]. The AGA states that statins are safe to treat hyperlipidemia in NAFLD and NASH patients (1B evidence) and guidelines from the European Association for the Study of Liver Disease state that statins "may be confidently used" to treat hyperlipidemia to prevent cardiovascular disease (CVD) in NAFLD patients. Several trials have demonstrated survival benefit with statins in NAFLD, including an RCT of 1600 patients with known CVD, hyperlipidemia, and NAFLD. This resulted in a 68% relative-risk reduction (P<0.0001) and a number needed to treat of 15 per year to prevent one cardiovascular event [21]. Other medications have been examined including metformin for which little data exists to show any improvement in the histologic markers of NAFLD or NASH[22].

Several investigational therapies are being examined for the treatment of NAFLD. Obetocholic acid, (farnesoid X receptor agonist) which reduces bile acid secretion and inflammatory cytokines allowing for improved glucose and lipid homeostasis, is among the best vetted. In a small double-blinded RCT with 229 non-diabetic, non-cirrhotic patients, there was a 24 percentage point improvement over placebo in steatohepatitis scores (P<0.0002) with statistically significant improvement

in inflammation and fibrosis[23]. Liraglutide has been shown to have some resolution of NASH and fewer patients who progressed to fibrosis, however it failed to show a statistically significant change in the mean NAFLD activity score[24].

Conclusions:
NAFLD is a growing epidemic worldwide. AI/AN populations have higher than average rates of NAFLD risk factors and increased risk of death from liver disease, making NAFLD an important topic for practitioners in the IHS. Evidence for pharmaceutical treatment of NAFLD is still lacking, however promising drugs targeting disease specific factors are on the horizon. At this time, there is not enough data to support any changes to the National Core Formulary, however it is critical that the safety and efficacy of statins in NAFLD is emphasized. Likewise, the treatment of NAFLD associated disease such as cardiovascular disease and T2DM should remain at the forefront of therapy.

For questions about this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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Indian Health Service
National Pharmacy and Therapeutics Committee
Polycystic Ovarian Syndrome
NPTC Formulary Brief
February Meeting 2017

Background:
Polycystic Ovarian Syndrome (PCOS) is a metabolic disorder affecting between 5 and 10 percent of women of childbearing age[1]. Ovulatory dysfunction, hyperandrogenism and polycystic ovaries are hallmark symptoms of PCOS. Additionally, many women affected also exhibit cutaneous manifestations (acne), hyperinsulinemia, infertility, hirsutism, dyslipidemia, obstructive sleep apnea, depression and anxiety[2-5]. The National Pharmacy & Therapeutics Committee (NPTC) reviewed available therapies for PCOS. As a result of the clinical review and NPTC discussion, oral medroxyprogesterone was added to the National Core Formulary (NCF).

Discussion:
Determining an appropriate treatment plan for PCOS ultimately depends on the patient's goal. Patients who present with androgenic symptoms such as acne, hirsutism, and amenorrhea or oligomenorrhea may benefit from combined hormonal contraceptives (CHCs). The CHCs are considered first-line agents for PCOS management in patients not intending to conceive[2]. Combined hormonal contraceptives offer menstrual cycle regulation and endometrial protection as well as benefits against clinical and biochemical hyperandrogenism. No single formulation is recommended over another, however regimens with lower estrogen/progestin doses may confer benefit over other regimens. Estrogen increases the risk of thromboembolism (VTE), especially in overweight women. Patients at risk for adverse effect due to estrogen (e.g., history of VTE, hypertension, smokers) should have "progestin-only" alternatives considered. Metformin may be used as second-line therapy (after CHCs) for menstrual cycle regulation. Cosmetic procedures such as blended electrolysis and photoepilation are sometimes effective for mild to moderate hirsutism. More severe cases of hirsutism may respond to spironolactone, but should be used cautiously due to adverse effects[2, 6].

Many women with PCOS develop insulin resistance particularly those who are inactive and/or obese, which can lead to Type 2 diabetes over time. Additionally, because of the increased likelihood of metabolic disorders, women with PCOS should be screened, treated, or appropriately referred if certain comorbidities (i.e., Type 2 diabetes, impaired glucose tolerance, hypertension, dyslipidemia, obesity, mood disorders, obstructive sleep apnea) are present. Weight loss using exercise and a calorie-restricted diet is recommended to reduce cardiovascular risks for obese women with PCOS, as well as those with Type 2 diabetes or impaired glucose tolerance (IGT). Metformin is recommended for PCOS patients diagnosed with IGT or Type 2 diabetes who are inadequately managed by diet and exercise. Metformin has been demonstrated to have no effect on cutaneous manifestations such as acne and has not been shown to improve pregnancy outcomes[2, 4].

The 2013 Endocrine Society guidelines for PCOS recommend clomiphene or a comparable estrogen modulator (e.g., letrozole) as first-line therapy for ovulation induction in women experiencing infertility[2]. A recent meta-analysis involving nine randomized controlled trials comparing letrozole and clomiphene (with or without adjuncts in 1 or both arms) followed by timed intercourse found the birth rate higher in the letrozole group (OR 1.64; 95% CI: 1.32 - 2.04, n=1783, I2=3%)[7]. The American College of Gynecology considers exogenous gonadotropins as a second-line therapy for ovulation induction[8,9].

Key points:
- CHCs are first-line agents for PCOS management to address both menstrual abnormalities and hyperandrogenism (acne/hirsutism). Progestin-only contraceptives or metformin may be considered as second-line therapies
- Weight loss is recommended as a first-line therapy for obese women with PCOS
- Clomiphene or a comparable estrogen modulator (e.g., letrozole) is recommended as first-line for ovulatory dysfunction resulting in infertility
- Metformin is recommended for women with PCOS diagnosed with Type 2 diabetes or OGT who fail diet and exercise

- Antiandrogens (spironolactone, finasteride, etc.) are suggested only in managing severe hirsutism or when CHCs are contraindicated

Findings:
Polycystic Ovary Syndrome is a common condition in women, often accompanied by a multitude of metabolic comorbidities and infertility. Review of medications on the NCF show there are sufficient pharmacotherapies to adequately address patients with PCOS and associated complications. Medroxyprogesterone is currently on the NCF as injection only to provide extended duration contraception. The NPTC added the oral formulation of medroxyprogesterone to offer providers an option for managing secondary physiologic amenorrhea and other conditions for which the injection may not be suitable.

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