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**Contents**

**Bimonthly Volume 2 Number 1 February 6, 2011**

**EDITORIAL**

- 1 Is there any progress in the treatment of non-alcoholic fatty liver disease?  
*Tsochatzis EA, Papatheodoridis GV*

**CASE REPORT**

- 6 Digital ischemic necrosis caused by pegylated interferon in a patient with  
hepatitis C  
*Hashash JG, Tackett SA, McAdams DJ*

## Contents

**ACKNOWLEDGMENTS** I Acknowledgments to reviewers of *World Journal of Gastrointestinal Pharmacology and Therapeutics*

**APPENDIX** I Meetings  
I-V Instructions to authors

**ABOUT COVER** Hashash JG, Tackett SA, McAdams DJ. Digital ischemic necrosis caused by pegylated interferon in a patient with hepatitis C.  
*World J Gastrointest Pharmacol Ther* 2011; 2(1): 6-8  
<http://www.wjgnet.com/2150-5349/full/v2/i1/6.htm>

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## Is there any progress in the treatment of non-alcoholic fatty liver disease?

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### Abstract

Despite the fact that non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis, are becoming increasingly prevalent in the industrialised countries, there are no licensed pharmacological treatments for them. Weight loss and life modifications, antioxidant therapies and insulin-sensitising agents are the current treatment strategies and have all been tested with inconclusive results. Low sample numbers, inadequate treatment duration and invalid surrogate markers for treatment response might all account for these results. As NAFLD is a systemic rather than a liver disease, future trials should address the patient as a whole and also address cardiovascular risk factors.

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**Key words:** Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Weight loss; Pioglitazone; Metformin

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### INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis (NASH), are becoming increasingly prevalent in industrialised countries, along with the epidemic of obesity<sup>[1]</sup>. The prevalence of NAFLD is estimated to be 10%-25% in the Western world, while the corresponding prevalence of NASH ranges from 2%-7%<sup>[2-16]</sup> (Table 1). Insulin resistance and metabolic syndrome have been implicated both in the pathogenesis and disease progression of NAFLD<sup>[17-19]</sup>, causing, among other symptoms, increased free fatty acid influx to the liver, oxidative stress, mitochondrial toxicity, deregulation of adipokines and subsequently inflammation and fibrosis<sup>[20-22]</sup> (Figure 1). It has become clear that NAFLD is not a benign non-progressive disease, as originally suggested, but results in increased morbidity and mortality, as shown in several studies with longitudinal follow-up<sup>[23-25]</sup>. It is notable that cardiovascular events and non liver-related deaths were the main cause of mortality in patients studied<sup>[24,25]</sup>. This is not surprising given the high prevalence of metabolic syndrome and its components in NAFLD patients. Currently, there are no licensed therapies for NAFLD, despite the abundance of clinical trials. In this review we will explore the current status of such treatments and propose a future research agenda.

### TREATMENT STRATEGIES FOR NAFLD

The existing treatment strategies for NAFLD can be divided into three main categories: weight loss and life-style modifications, insulin-sensitising agents and antioxidant therapies. As a general comment, most studies suffer from inadequate patient numbers, lack of randomisation and use of markers for treatment response other than histology. It

Table 1 Prevalence of non-alcoholic fatty liver disease in different countries

Author	Country	Population	n	Prevalence of NAFLD (%)	Methods of diagnosis
Fan <i>et al</i> <sup>[5]</sup> , 2007	China	Normal	14 646	14	US
Papatheodoridis <i>et al</i> <sup>[8]</sup> , 2007	Greece	Normal	3063	18	Liver enzymes
Zelber-Sagi <i>et al</i> <sup>[16]</sup> , 2006	Israel	Normal	326	30	US
Bedogni <i>et al</i> <sup>[3]</sup> , 2007	Italy	Normal	598	20	US
Targher <i>et al</i> <sup>[12]</sup> , 2007	Italy	T2DM	2839	70	US
Sorrentino <i>et al</i> <sup>[11]</sup> , 2004	Italy	Bariatric surgery	80	72	Biopsy
Hamaguchi <i>et al</i> <sup>[6]</sup> , 2005	Japan	Normal	4401	18	US
Yamamoto <i>et al</i> <sup>[15]</sup> , 2007	Japan	Normal	263	18	US
Park <i>et al</i> <sup>[9]</sup> , 2006	Korea	Normal	6648	19	US
Roesch-Dietlen <i>et al</i> <sup>[10]</sup> , 2006	Mexico	Metabolic syndrome	337	16	US
Browning <i>et al</i> <sup>[4]</sup> , 2004	USA	Normal	2287	31	MRS
Tran <i>et al</i> <sup>[13]</sup> , 2006	USA	Living donors	70	38.5	Biopsy
Kunde <i>et al</i> <sup>[7]</sup> , 2005	USA	Bariatric surgery	233	97	Biopsy
Weston <i>et al</i> <sup>[14]</sup> , 2005	USA	Chronic liver disease	742	39	US/CT

NAFLD: Non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; US: Ultrasonography, MRS: Magnetic resonance spectroscopy; CT: Computerized tomography.

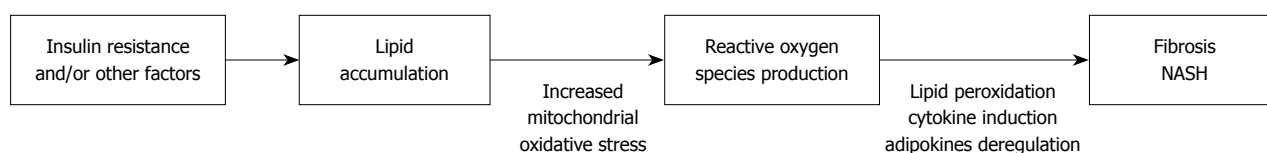


Figure 1 Mechanisms of progression from normal liver to non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. NASH: Non-alcoholic steatohepatitis.

is not, therefore, surprising that they are often inconclusive and fail to show any treatment effect. Currently, there is no licensed pharmacological treatment for NASH and patients are usually advised to lose weight and exercise.

### Weight loss

As NAFLD is most commonly associated with obesity<sup>[26]</sup>, weight loss is a reasonable initial step towards treating this condition. The theoretical advantages of weight loss include decreasing insulin resistance and, if combined with exercise, increasing muscle insulin sensitivity. Despite the pathophysiological evidence of such an approach, there has been only one randomised control trial (RCT) of weight loss in patients with NAFLD, with a sample size of just 31 patients<sup>[27]</sup>. Patients in the intervention group were targeted for a 7%-10% weight reduction through intensive lifestyle intervention and were monitored for a year with initial and end-of-treatment liver biopsies. Although there was significant improvement in the NASH histological activity score (NAS) in the intervention group and a significant correlation of percent weight loss with improvement in NAS, no significant improvement in fibrosis was documented<sup>[27]</sup>. All other trials have been non-randomised, with no control group and have usually comprised selected patients or case series<sup>[28]</sup>. However, improved liver biochemistry and even resolution of stigmata of liver disease have been shown with weight loss in selected overweight patients<sup>[29,30]</sup>. The main concerns with this strategy include the feasibility of maintaining weight loss over a prolonged time course. Furthermore, rapid

weight loss in morbidly obese can actually worsen fibrosis<sup>[31]</sup>. Therefore, counselling should aim towards gradual weight loss with appropriate life-style modifications and behavioural therapies that would allow weight loss to be maintained over the course of time<sup>[28]</sup>.

Orlistat, which is a reversible inhibitor of gastric and pancreatic lipase and thus prevents the absorption of diet triglycerides, is used for weight loss and has been tested in the management of NASH in a small RCT<sup>[32]</sup>. Although patients who achieved a weight loss of > 9% improved in biochemistry and inflammation measures, there were no significant differences in weight loss between the orlistat and the placebo group.

Bariatric surgery is normally limited to morbidly obese patients and is considered as a therapeutic option in selected patients with NASH<sup>[33]</sup>. However, the recent Cochrane meta-analysis found that evidence on the potential benefits and risks of bariatric surgery is derived from cohort studies and is, therefore, not conclusive<sup>[34]</sup>.

It should be also underlined that in addition to food quantity, quality also matters. Results from cohort studies suggest that patients with NAFLD have higher consumption of saturated fatty acids and cholesterol, higher consumption of soft drinks that contain fructose and lower consumption of vitamins A and E<sup>[35-38]</sup>. Therefore, counselling regarding the quality of calories consumed should also be offered. Lipid lowering therapies are safe in patients with liver disease<sup>[39]</sup> and preliminary evidence suggests that they might prove beneficial in patients with NAFLD<sup>[40]</sup>.



### Anti-oxidant therapies

Ant-oxidant therapies have been tried for NAFLD on the theoretical basis that oxidative stress is involved in the pathogenesis of the disease. The results of trials are inconclusive and contradictory, probably because of the small patient numbers. A small pilot trial of pentoxifylline showed improvement in aminotransferases in the 11 patients who completed the 1-year course of medication, although no follow-up histological evaluation was available<sup>[41]</sup>. Ursodeoxycholic acid failed to show any benefit after two years of therapy in a RCT of 165 patients<sup>[42]</sup>. A combination of vitamins E and C taken for 6 mo improved fibrosis but not necroinflammation or liver enzymes<sup>[43]</sup>. A recent RCT, published in abstract form, of vitamin E or pioglitazone or placebo, showed significant improvement in the NAS score of patients who received vitamin E compared to the other two groups. However, no improvement in fibrosis was documented<sup>[44]</sup>. However, other small RCTs have failed to demonstrate any treatment effect of vitamin E<sup>[45,46]</sup>.

### Insulin-sensitising therapies

As insulin resistance is considered the main underlying mechanism and predisposing condition for NASH, treatment strategies targeting insulin resistance are a main focus of the current research agenda. Metformin and thiazolidinediones which are licensed antidiabetic medications that target peripheral and hepatic insulin resistance have been used in the treatment of patients with NASH.

The first evidence of the potential effect of metformin came from a small cohort study of 20 patients with no follow-up histological evaluation, in which transaminase values and insulin sensitivity improved after 4 mo of treatment<sup>[47]</sup>. A small Turkish RCT of 36 patients, comparing metformin with no treatment and with 6 mo follow up, confirmed the improvement in transaminases but failed to demonstrate any effect on liver histology<sup>[48]</sup>. An RCT of metformin *vs* vitamin E *vs* no treatment in patients who were all assigned to prescriptive diet showed a significantly higher rate of transaminase normalization as well as a significant improvement in necroinflammation and fibrosis compared to baseline biopsy in the metformin group<sup>[45]</sup>. However, liver biopsy was not performed in the control group and it is thus difficult to assess if the histological improvement was due to weight loss or metformin. Therefore, although metformin is a safe and promising medication, it has not yet been assessed in properly designed and adequately powered RCTs.

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor- $\gamma$  agonists that improve insulin resistance in liver, muscle and adipose tissue. The licensed TZDs, pioglitazone and rosiglitazone, have been both tried in RCTs in patients with NAFLD. The two drugs appear to have different effects on lipid metabolism, as rosiglitazone has no effect on de novo hepatic lipogenesis and plasma triglycerides, while pioglitazone actually decreases both<sup>[49]</sup>. An RCT of 45 mg of pioglitazone *vs* placebo for 6 mo, showed significant improvements in steatosis, necroinflammation and ballooning in the treatment group although improvement in fibrosis did not reach

statistical significance ( $P = 0.008$ )<sup>[50]</sup>. These encouraging results provided the rationale for further RCTs of longer duration. A lower dose of pioglitazone (30 mg/d) improved fibrosis and hepatocellular injury compared to placebo in an RCT of 74 non-diabetic patients with NASH. However, the biggest RCT to date, with a follow-up of 2 years, failed to show any significant histological improvement in the pioglitazone group (30 mg/d) compared to the placebo group<sup>[44]</sup>. RCTs on rosiglitazone, of one and two year duration, have shown no significant effects on liver histology<sup>[51,52]</sup>.

## CRITICAL APPRAISAL AND FUTURE DIRECTIONS

Although NAFLD is an increasingly prevalent disease, there is a lack of approved therapies for it. There are several reasons for this absence of effective therapies.

Firstly, most published studies are not adequately powered to demonstrate significant treatment effects and some of the non-significant findings that they report might actually be type II errors.

Secondly, treatment effects are assessed after 6 or 12 mo of therapy duration, which is an arbitrary time cut-off and might be inadequate. Although such treatment durations have been successfully implemented for chronic viral hepatitis B and C infections, these conditions have totally different pathophysiology of liver injury and probably a more rapid clinical course than NAFLD<sup>[25,53]</sup>.

Thirdly, the NAS activity score is increasingly being used as a surrogate marker to assess therapeutic effect. However, this score is not a valid surrogate marker for NAFLD as it does not take fibrosis into account<sup>[54]</sup>. Existing studies suggest that the presence and severity of fibrosis actually dictate long-term mortality in patients with NAFLD<sup>[25]</sup>, while the NAS score is an untested, if not irrelevant, surrogate marker<sup>[55]</sup>. Therefore, although improvements in the NAS score not accompanied by improvements in fibrosis would currently classify a study as having a positive result, the true value of these studies is unknown.

Fourthly, metformin remains an untested therapeutic option, despite preliminary evidence of its benefits. This may be because it is a cheap and well established drug and there is, therefore, limited interest in funding and any RCT would have to be investigator-initiated.

Lastly, and most importantly, NAFLD is a systemic rather than a liver disease. Indeed, cardiovascular disease is the main cause of death in NAFLD patients<sup>[24]</sup>. Therefore, all risk factors should be globally assessed and therapeutic strategies should ideally target the patient as a whole rather than liver-specific disease manifestations alone.

Future trials should recruit larger number of patients for a longer treatment period. The recent pioglitazone or vitamin E for nonalcoholic steatohepatitis RCT demonstrated that insulin resistance might not be the driving force behind fibrosis progression in NAFLD patients and that combination therapy targeting different mechanisms might represent the optimal strategy for NAFLD<sup>[44]</sup>. Angiotensin

receptor blockers and angiotensin converting enzyme inhibitors have shown experimental evidence of effect and are already tested in ongoing RCTs<sup>[56]</sup>. Other potential future treatments include incretin analogues, silymarin, dietary factors such as omega-3 fatty acids and polyunsaturated fatty acids and even molecular targets<sup>[56,57]</sup>. As evidence is constantly accumulating, it is a matter of time before effective treatments for NAFLD become available.

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## Digital ischemic necrosis caused by pegylated interferon in a patient with hepatitis C

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### Abstract

Pegylated interferon plus ribavirin remains the first-line treatment for patients with hepatitis C virus (HCV). Interferon  $\alpha$  has the most extensive clinical application and is used for the treatment of chronic hepatitis B virus and hepatitis D virus as well as acute and chronic HCV infections. The attachment of polyethylene glycol to interferon increases its half-life by reducing the rate of absorption after injection, reducing renal and cellular clearance and also decreasing immunogenicity. In this case report, we have described a patient with chronic hepatitis C who developed ischemic necrosis of her fingertips after completing her third course of pegylated interferon and ribavirin. The patient underwent a very extensive workup in order to determine the underlying cause of her digital ischemia which was finally determined to be secondary to the use of pegylated interferon.

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**Key words:** Pegylated interferon; Interferon; Hepatitis C; Necrosis; Ischemia

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### INTRODUCTION

Almost 170 million individuals are affected by chronic hepatitis C viral infection worldwide. The first-line treatment for such patients includes a combination of pegylated interferon and ribavirin for a total of 24 or 48 wk, depending on the viral genotype. Up to 70% of patients experience fatigue, myalgias and headache as a side effect of the above mentioned combination therapy<sup>[1]</sup>. Other more adverse side effects may also occur. These include depression, suicidal ideations, cardiovascular events and hemolytic anemia and are fortunately less frequently encountered<sup>[2]</sup>. There have been a few case reports of vascular events occurring in patients treated with interferon  $\alpha$ . Regardless, prolonged digital cyanosis or necrosis associated with interferon is rare and none of the reported cases involved pegylated interferon.

### CASE REPORT

A 53-year-old female with chronic hepatitis C genotype-1a presented to an outside hospital with a chief complaint of chest pain. The patient's symptoms occurred one month after completing her third course of pegylated interferon  $\alpha$ -2a (Pegasys injection 180 mcg) and ribavirin (600 mg). Of note, she had previously tolerated these treatment regimens without any acute complications. The chest pain was accompanied by shortness of breath and bluish

discoloration of her right index fingertip. While her chest x-ray revealed a small pleural effusion, the remainder of her work-up including electrocardiography, computed tomography (CT) scan of the chest with contrast, transesophageal echocardiogram and cardiac catheterization was unremarkable. The cause of the finger discoloration was undetermined and the patient was discharged home.

A few days later, the discoloration of the patient's right index finger worsened and the right middle and left index fingertips also became cyanotic and painful. On arrival at our institution, the patient was afebrile and chest pain free. The affected fingers were cool and cyanotic; however there were no deficits in sensation, strength or radial pulses or other notable skin findings. Initial work-up included basic labs, C3, C4, blood cultures, rheumatoid factor and cold agglutinins which were negative. Erythrocyte Sedimentation Rate was 20 and C-Reactive Protein was 5.3. Antinuclear antibody was measured at 1:40 with a speckled pattern. Autoantibody studies for anti-dsDNA, anti-smith, Anti-neutrophil cytoplasmic antibody, anti-topoisomerase, anti-centromere, anti-RNA PolIII, anti-Ro, anti-La, anti-RNP, anti-Jo1 and cryoglobulins were all negative. An upper extremity arterial Doppler ultrasound showed patent radial and ulnar arteries with vasospasm of the palmar arcades bilaterally. Vasospasm can be detected on ultrasound by spectral analysis with exposure to cold to provoke spasm and heat to relieve the spasm. In the presence of vasospasm, the flow pattern is extremely pulsatile. In retrospect, it was unclear whether or not her initial presentation with chest pain was a result of coronary vasospasm possibly related to the vasospastic process that was noted in her upper extremities.

The patient had multiple complications during her hospitalization and, interestingly, she developed hemolytic anemia and thrombocytopenia. prothrombin time, partial thromboplastin time, fibrinogen and fibrin degradation product levels were within normal limits. An ADAMTS13 level was borderline low which was attributed to inflammation rather than to thrombotic thrombocytopenic purpura (TTP). Hypercoagulable studies showed no clotting diathesis. Anti-hepatitis C virus (HCV) Ab was positive but HCV polymerase chain reaction was < 30 IU/mL. Human immunodeficiency virus, hepatitis A virus and hepatitis B virus (HBV) serologies were negative.

After the patient's condition stabilized, attention returned to her ischemic fingers (Figure 1). Biopsy of her fingertips revealed a thrombotic coagulopathy. CT angiography of the upper extremities with pre and post dilatation images were obtained and showed no abnormalities. Invasive angiography, however, revealed occlusions of the left 2nd proper digital arteries and the right 2nd and 3rd proper digital arteries, without improvement after intra-arterial administration of papaverine, a vasodilator. Due to necrosis of her right index, right middle and left index fingers, the patient underwent amputation of those digits as well as radial and ulnar digital nerve surgery in attempt to prevent her pain from progressing. Surgical pathology reported ischemic necrosis of skin and adjacent soft tissues and prominent thickening of small and medium



**Figure 1** Pegylated-interferon  $\alpha$  induced digit necrosis in a female patient receiving treatment for hepatitis C virus.

sized vessels with focal fibrin thromboemboli. There was no evidence of vasculitis. Grocott and periodic acid schiff with digestion (PASD) stains showed bacterial colonization as well as fungal hyphae in the necrotic tissue. No viral stains were performed.

## DISCUSSION

Causes of digital ischemic necrosis are most commonly due to vasculitis, either autoimmune or drug-induced<sup>[3]</sup>. However, our patient had a negative rheumatological work-up and biopsy showed no inflammatory changes. The absence of cold agglutinins, although insensitive, did further assure us that this was less likely to be cryoglobulinemic digital ischemia. Digital ischemia can also be attributed to embolic phenomena such as endocarditis or cholesterol emboli; however these seem unlikely based on the work-up and the timing of the angiography. Our patient's necrosis was due to microvascular occlusion. While the exact mechanism is not yet known, interferon treatment has led to microthrombi and endothelial cell injury without inflammatory cell infiltration in mouse models<sup>[4]</sup>. Based on this patient's presentation and the extensive work-up, we concluded that the patient developed digital ischemic necrosis as a result of treatment with pegylated interferon  $\alpha$ .

Pegylated interferon plus ribavirin remains the first-line treatment for patients with HCV<sup>[5]</sup>. Interferons are a family of cytokines that regulate resistance to viral infections, enhance innate and acquired immune responses and modulate normal and tumor cell survival and death. In-



terferon  $\alpha$  has the most extensive clinical application and is currently primarily used for the treatments of chronic HBV and hepatitis D virus as well as acute and chronic HCV<sup>[6]</sup>. The attachment of polyethylene glycol to interferon increases its half-life by reducing the rate of absorption after injection. This in turn reduces renal and cellular clearance and also decreases immunogenicity, allowing pegylated interferon to achieve higher steady-state concentrations in the body. Randomized clinical trials have shown that pegylated interferon has a better sustained viral response rate when compared to standard interferon. Moreover, pegylated interferon tends to have less flu-like and depressive side effects.

Dermatological complications are known to occur with both HCV and interferon; however exactly which are due to HCV and which are due to interferon is not always clear. HCV has been isolated from biopsies of skin lesions from mixed cryoglobulinemia, lichen planus and psoriasis. Association of HCV with porphyria cutanea tarda and necrolytic acral erythema also occurs. We were unable to find any reports of HCV leading to digital necrosis. While more than 80% of patients receiving interferon will experience side effects (mostly flu-like), reports of digital ischemia are rare<sup>[7]</sup>. It is possible however, that interferon-related digital ischemia is under-reported. Al-Zahrani described a wide variety of vascular events associated with the use of interferon  $\alpha$ , including Raynaud's phenomenon, digital ulcerations and gangrene, pulmonary vasculitis and TTP/hemolytic uremic syndrome (HUS)<sup>[8]</sup>. In one series of 25 patients being treated with interferon  $\alpha$  for chronic myeloid leukemia (CML), 13 (52%) reported that they had experienced symptoms consistent with Raynaud's phenomenon<sup>[9]</sup>. Interestingly, there has also been a report of intestinal vasculitis with subsequent ischemia due to arteritis and arterial occlusion in a patient receiving pegylated interferon<sup>[10]</sup>. Regardless, prolonged digital cyanosis or necrosis associated with interferon is rare and none of these involved pegylated interferon or treatment for HCV.

In conclusion, given the high prevalence of chronic

HCV infection, it is of utmost importance for physicians to be aware of the potential side effects of HCV therapy as many of those side effects lead to serious and detrimental consequences. In our patient, treatment with pegylated interferon  $\alpha$  caused necrosis of the digits necessitating amputation.

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## Meetings

### Events Calendar 2011

January 14-15, 2011  
AGA Clinical Congress of  
Gastroenterology and Hepatology:  
Best Practices in 2011, Loews Miami  
Beach Hotel, Miami, FL,  
United States

January 27, 2011  
Symposium of the Swiss Society  
of Pharmacology and Toxicology,  
Advances in Pharmacology-  
Psychopharmacology, Bern,  
Switzerland

February 17-20, 2011  
APASL 2011 - The 21st Conference  
of the Asian Pacific Association for  
the Study of the Liver, Bangkok,  
Thailand

February 26-March 01, 2011  
Canadian Digestive Diseases Week,

Westin Bayshore, Vancouver, British  
Columbia, Canada

March 02-05, 2011  
American Society for Clinical  
Pharmacology and Therapeutics  
2011 Annual Meeting, Dallas, TX,  
United States

March 22-24, 2011  
11th South East Asian Western  
Pacific Regional Meeting of  
Pharmacologists in conjunction  
with the 84th Annual Meeting of the  
Japanese Pharmacological Society,  
Yokohama, Japan

March 24, 2011  
Asia Pharma R&D Leaders 2011-the  
largest and premier pharma R&D  
summit in China, Shanghai, China

April 06-08, 2011  
Third Latin American Symposium  
on Gastrointestinal Oncology -  
Chilean Foundation for Oncology  
Development Joint Symposium,  
Vina Del Mar, Chile

April 20-23, 2011  
9th International Gastric Cancer

Congress, COEX, World Trade  
Center, Samseong-dong, Gangnam-  
gu, Seoul 135-731, South Korea

May 22-25, 2011  
2011 American Academy of  
Veterinary Pharmacology &  
Therapeutics 17th Biennial  
Symposium, 610 Langdon Street,  
Madison, WI, United States

May 24-27, 2011  
Meeting joint between CSPT and the  
Canadian Society for Pharmaceutical  
Sciences, the Controlled Release  
Society and the Natural Health  
Products Research Society of  
Canada, Montreal, Quebec, Canada

June 26-29, 2011  
10th European Association for  
Clinical Pharmacology and  
Therapeutics Congress, Budapest,  
Hungary

September 11-13, 2011  
40th Annual Meeting of American  
College of Clinical Pharmacology,  
Crowne Plaza Chicago O'Hare  
Hotel, Chicago, IL, United States

October 02-06, 2011  
12th International Congress of  
Therapeutic Drug Monitoring  
& Clinical Toxicology, Stuttgart,  
Germany

October 06-07, 2011  
IV InterAmerican Oncology  
Conference: Current Status and  
Future of Anti-Cancer Targeted  
Therapies, Buenos Aires, Argentina

November 11-12, 2011  
Falk Symposium 180, IBD 2011:  
Progress and Future for Lifelong  
Management, 1-12-33 Akasaka,  
Minato-ku, Tokyo 107-0052, Japan

December 01-04, 2011  
International Symposium On Ocular  
Pharmacology And Therapeutics,  
Hilton Vienna, Vienna, Austria

December 04-07, 2011  
Perth 2011 joint Meeting between  
the Australian Physiological Society,  
the Australian Society of Clinical  
and Experimental Pharmacologists  
and the High Blood Pressure  
Research Council of Australia, Perth  
Convention Centre, Perth, WA,  
Australia



## Instructions to authors

### GENERAL INFORMATION

*World Journal of Gastrointestinal Pharmacology and Therapeutics* (World J Gastrointest Pharmacol Ther, WJGPT, online ISSN 2150-5349, DOI: 10.4292), is a bimonthly, open-access (OA), peer-reviewed journal supported by an editorial board of 188 experts in gastrointestinal pharmacology and therapeutics from 36 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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### Aims and scope

The major task of WJGPT is to rapidly report the most recent results in basic and clinical research on gastrointestinal pharmacology & therapeutics, including the effects of drugs on the gastrointestinal, pancreatic and hepatobiliary systems, particularly with relevance to clinical practice. WJGPT accepts papers on the following aspects related to gastroenterology or hepatology: (1) Clinical pharmacological research articles on specific drugs, concerning with pharmacodynamics, pharmacokinetics, toxicology, clinical trial, drug reactions, drug metabolism and adverse reaction monitoring, *etc.*; (2) Research progress of clinical pharmacology; (3) Introduction and evaluation of new drugs; (4) Experiences and problems in applied therapeutics; (5) Research and introductions of methodology in clinical pharmacology; and (6) Guidelines of clinical trial. Specifically, this journal welcome research and review articles associated with both Western medicine and Chinese herbs as well as their combinations in basic and clinical application.

### Columns

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### Name of journal

*World Journal of Gastrointestinal Pharmacology and Therapeutics*

### CSSN

ISSN 2150-5349 (online)

### Indexing/abstracting

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### Published by

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## SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

### Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Redit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used,

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**Title:** Title should be less than 12 words.

**Running title:** A short running title of less than 6 words should be provided.

**Authorship:** Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/..."; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g.  $6.92 \pm 3.86$  vs  $3.61 \pm 1.67$ ,  $P < 0.001$ ; CONCLUSION (no more than 26 words).

### Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

### Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: [http://www.wjgnet.com/2150-5349/g\\_info\\_list.htm](http://www.wjgnet.com/2150-5349/g_info_list.htm).

### Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: <http://www.wjgnet.com/1007-9327/13/4520.pdf>; <http://www.wjgnet.com/1007-9327/13/4554.pdf>; <http://www.wjgnet.com/1007-9327/13/4891.pdf>; <http://www.wjgnet.com/1007-9327/13/4986.pdf>; <http://www.wjgnet.com/1007-9327/13/4498.pdf>. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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### Notes in tables and illustrations

Data that are not statistically significant should not be noted. <sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01 should be noted (*P* > 0.05 should not be noted). If there are other series of *P* values, <sup>c</sup>*P* < 0.05 and <sup>d</sup>*P* < 0.01 are used. A third series of *P* values can be expressed as <sup>e</sup>*P* < 0.05 and <sup>f</sup>*P* < 0.01. Other notes in tables or under illustrations should be expressed as <sup>1</sup>F, <sup>2</sup>F, <sup>3</sup>F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

### Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

## REFERENCES

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Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

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### Format

#### Journals

*English journal article (list all authors and include the PMID where applicable)*

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

*Chinese journal article (list all authors and include the PMID where applicable)*

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

*In press*

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID: 2516377 DOI: 10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]

*No author given*

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI: 10.1136/bmj.325.7357.184]

*Volume with supplement*

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI: 10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI: 10.1097/00003086-200208000-00026]

*No volume or issue*

- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

### Books

*Personal author(s)*

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

**Patent** (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

### Statistical data

Write as mean  $\pm$  SD or mean  $\pm$  SE.

### Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as  $\chi^2$  (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

### Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h, blood glucose concentration, *c* (glucose)  $6.4 \pm 2.1$  mmol/L; blood CEA mass concentration, *p* (CEA) =  $8.6 \pm 24.5$   $\mu$ g/L; CO<sub>2</sub> volume fraction, 50 mL/L CO<sub>2</sub>, not 5% CO<sub>2</sub>; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: [http://www.wjgnet.com/2150-5349/g\\_info\\_20100315090437.htm](http://www.wjgnet.com/2150-5349/g_info_20100315090437.htm).

### Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to

the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

### Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, etc.

Restriction enzymes: *EcoRI*, *HindIII*, *BamHI*, *KhoI*, *KpnI*, etc.

Biology: *H. pylori*, *E. coli*, etc.

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