

## Electrocardiograms changes in children with functional gastrointestinal disorders on low dose amitriptyline

Ashish Chogle, Miguel Saps

Ashish Chogle, Miguel Saps, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ann and Robert Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, United States

Author contributions: Chogle A contributed to analysis and interpretation of data, drafting of the manuscript and revision of the manuscript; Saps M provided the conception and design, acquisition of data and revision of the manuscript.

Correspondence to: Ashish Chogle, MD, MPH, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ann and Robert Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, 225 E Chicago Ave, Chicago, IL 60611, United States. [achogle@luriechildrens.org](mailto:achogle@luriechildrens.org)  
Telephone: +1-312-2274000 Fax: +1-312-2279645

Received: December 20, 2013 Revised: March 28, 2014

Accepted: May 28, 2014

Published online: August 28, 2014

### Abstract

**AIM:** To study the effects of low dose amitriptyline on cardiac conduction in children.

**METHODS:** Secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating low dose amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and irritable bowel syndrome according to the Rome II criteria. Children 8-17 years of age were recruited from the pediatric gastroenterology clinics of 6 tertiary care centers in the United States. The electrocardiograms (EKGs) done prior to initiation of amitriptyline and 1 mo after initiation of amitriptyline were examined. The changes in cardiac conduction were evaluated in patients and controls.

**RESULTS:** Thirty children were included in the study. There were 12 patients, ages 9-17 years of both genders, in the amitriptyline treatment group and 18 patients, ages 9-17 years of both genders, in the placebo

treatment group. None of the patients had any baseline EKG abnormality. Amitriptyline use was associated with an increase in heart rate ( $P = 0.024$ ) and QTc interval ( $P = 0.0107$ ) as compared to pre-EKGs. Children in the placebo group were also noted to present a statistically significant increase in QTc interval ( $P = 0.0498$ ). None of the patients developed borderline QTc prolongation or long-QT syndrome after they were started on amitriptyline.

**CONCLUSION:** The study findings suggest that once patients with functional gastrointestinal disorders have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for re-evaluation of cardiac conduction after starting low dose amitriptyline.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Amitriptyline; Electrocardiogram; Children; Abdominal pain related-functional gastrointestinal disorders

**Core tip:** Information on electrocardiogram changes in children who are on low dose amitriptyline for treatment of abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) is sparse. To better understand the effects of low dose amitriptyline on cardiac conduction in children, we reviewed the electrocardiogram findings before and after initiation of amitriptyline. We found that use of low dose amitriptyline in children with AP-FGIDs was not associated with clinically significant changes in cardiac conduction.

Chogle A, Saps M. Electrocardiograms changes in children with functional gastrointestinal disorders on low dose amitriptyline. *World J Gastroenterol* 2014; 20(32): 11321-11325 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i32/11321.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i32.11321>

## INTRODUCTION

Abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) are among the most common medical afflictions in childhood and adolescence<sup>[1,2]</sup>. The AP-FGIDs have been categorized by the Rome III criteria into irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD) and abdominal migraine (AM). These disorders have been shown to significantly affect the children's quality of life<sup>[1,2]</sup>. Tricyclic antidepressants (TCAs) like amitriptyline have played an important role in the treatment of pediatric psychiatric disorders. However, the increased risk of adverse cardiac events, sudden deaths in children and a black box warning by the FDA on the risk of suicidality have led to a decline in their use<sup>[3,4]</sup>. TCAs have now been relegated to second line status for treatment of depression. Studies in adults have shown benefit in using TCAs for treatment of AP-FGIDs<sup>[5-11]</sup>. Amitriptyline has not been found to be better than placebo for treatment of AP-FGIDs in children and is not approved for the treatment of FGIDs in children or adolescents, but its off label use is prevalent<sup>[12-15]</sup>. The dose of amitriptyline commonly used in the treatment of FGIDs in children is much lower than that used for depression. A dose-response association of TCAs has been demonstrated with QTc prolongation<sup>[16]</sup>. TCA overdose has been shown to cause conduction delays and prolonged corrected QT (QTc) in children<sup>[17]</sup>. There is limited data in the literature regarding the cardiac toxicity with therapeutic antidepressant doses of amitriptyline in children. Information on electrocardiogram (EKG) changes in children who are on low dose amitriptyline for treatment of FGIDs is sparse. To better understand the effects of low dose amitriptyline on cardiac conduction in children, we reviewed the EKG findings before and after initiation of amitriptyline in a multicenter study conducted by our group assessing the efficacy of amitriptyline in children with AP-FGIDs<sup>[14]</sup>.

## MATERIALS AND METHODS

This study was a secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and IBS according to the Rome II criteria<sup>[14]</sup>. In the original study children 8-17 years of age were recruited from the pediatric gastroenterology clinics of 6 tertiary care centers geographically dispersed in the United States: Children's Hospital of Pittsburgh (Pittsburgh, PA), Goryeb Children's Hospital at Atlantic Health System (Morristown, NJ), Kansas University Medical Center (Kansas City, KS), Children's Hospital of Boston (Boston, MA), Children's Hospital of Wisconsin (Milwaukee, WI), and Children's Memorial Hospital (Chicago, IL). In the current study only those patients in both groups (amitriptyline treatment and placebo groups) who had a standard 12-lead EKG before starting the study medication (pre-

EKGs) and a second EKG 1 mo after initiation of the medication (post-EKGs) were included. Only the centers located at Chicago, Pittsburgh and Boston required EKGs to be done prior to and after starting amitriptyline. Amitriptyline was dosed based on their weight: (1) < 35 kg-10 mg capsule by mouth daily; and (2)  $\geq$  35 kg-20 mg capsule by mouth daily. All EKGs were read by pediatric cardiologists at the respective study locations. We examined the effect of amitriptyline and placebo on heart rate (HR), PR, QRS, and QTc interval with the 2 tailed *t*-test using GraphPad statistical software.

A QTc interval at or above 480 ms in females or 470 ms in males was considered diagnostic of long-QT syndrome (LQTS)<sup>[14]</sup>. The diagnosis of borderline QT prolongation was given when a patient had a QTc value between 440 and 470 ms.

## RESULTS

Thirty children were included in the study. There were 12 patients (10 females), ages 9-17 years (10 patients were 10 years or older), in the amitriptyline treatment group and 18 patients (15 females), ages 9-17 years (16 patients were 10 years or older), in the placebo treatment group. Using the D'Agostino-Pearson test for normality, the data was found to have normal distribution. None of the patients had any baseline EKG abnormality. Amitriptyline use was associated with an increase in heart rate ( $P = 0.024$ ) and QTc interval ( $P = 0.0107$ ) as compared to pre-EKGs (Table 1). Children in the placebo group were also noted to present a statistically significant increase in QTc interval ( $P = 0.0498$ ) (Table 1). None of the patients developed borderline QTc prolongation or LQTS after they were started on amitriptyline.

## DISCUSSION

Amitriptyline at low doses is thought to work primarily by inducing pain tolerance through peripheral or central anti-nociceptive properties as well through its anticholinergic effects, and secondarily through its anxiolytic effects<sup>[8,14,18]</sup>.

A meta-analysis of adult studies showed that amitriptyline is beneficial in treatment of FGIDs in adults<sup>[5,7,8,19]</sup>. There have been 2 randomized controlled pediatric trials that have examined the efficacy and safety profile of low dose amitriptyline in treatment of FGIDs<sup>[13,14]</sup>. Both studies found no statistically significant differences between amitriptyline and placebo for most efficacy outcomes including improvement of abdominal pain (Bahar study found improvement exclusively in RLQ pain and a beneficial effect in quality of life). A review by the Cochrane's Group concluded that there was no evidence to support the use of amitriptyline for the treatment of abdominal pain-related FGIDs in children and adolescents<sup>[12]</sup>. Despite the lack of evidence of its efficacy, clinicians commonly prescribe amitriptyline to children with AP-FGIDs. Typically a 0.5-1 mg/kg per day dose of amitrip-

**Table 1** Effect of amitriptyline and placebo on cardiac conduction in children

Parameters	HR (beats/min)		PR (ms)		QRS (ms)		QTc (ms)	
	Pre EKG	Post EKG	Pre EKG	Post EKG	Pre EKG	Post EKG	Pre EKG	Post EKG
Drug								
mean $\pm$ SD	75.92 $\pm$ 9.44	85.2 $\pm$ 17.4	135 $\pm$ 12.97	134.5 $\pm$ 11.25	83.67 $\pm$ 6.81	85.33 $\pm$ 7.15	406.91 $\pm$ 12.6	418 $\pm$ 13.8
2 tailed <i>t</i> test <i>P</i> value		0.024 <sup>a</sup>		0.8429		0.2098		0.0107 <sup>a</sup>
Correlation coefficient - <i>r</i>		0.7367		0.7608		0.8084		0.4923
Placebo								
mean $\pm$ SD	69.22 $\pm$ 12.26	74.05 $\pm$ 10.06	132.6 $\pm$ 16.35	137.5 $\pm$ 21.53	86.7 $\pm$ 8.95	83.8 $\pm$ 8.98	415.5 $\pm$ 16.82	422.6 $\pm$ 18.53
<i>n</i>	18	18	18	18	18	18	18	18
2 tailed <i>t</i> test <i>P</i> value		0.0783		0.1394		0.0937		0.0498 <sup>a</sup>
Correlation coefficient - <i>r</i>		0.5343		0.7841		0.7037		0.6773

<sup>a</sup>*P* < 0.05, placebo group *vs* control group.

tyline to a maximum of 50 mg daily is used as opposed to 1-3 mg/kg per day used for depression in children<sup>[14]</sup>.

Amitriptyline activates cardiac ryanodine channels causing efflux of calcium from the sarcoplasmic reticulum<sup>[20]</sup>. As a result, amitriptyline is pro-arrhythmogenic and increases the risk of sudden cardiac death in patients with underlying heart disease and at doses above 100 mg daily<sup>[3]</sup>. Amitriptyline has been classified as a “conditional risk” drug for development of torsade de pointes<sup>[21]</sup>. Drugs with “conditional risk” have significant evidence of prolonging QT and causing torsade de pointes but only under certain conditions, such as excessive dose or drug interaction<sup>[22]</sup>. Some studies have documented changes in EKG tracings in children on the higher doses of amitriptyline used for depression<sup>[23,24]</sup>. These have included findings ranging of no changes in any of the tracings to increases in the heart rate, PR, QRS and QTc intervals. In a recent risk prevention study, the incidence of prolonged QTc interval in a subpopulation of children with IBS before the initiation of amitriptyline was found to be 0.4%, which is similar to the incidence of prolonged QTc in adult and adolescent athletes<sup>[25,26]</sup>. This study concluded that a screening EKG should always be performed on children with FGIDs, before initiating amitriptyline therapy<sup>[25]</sup>.

We found practice variation in conducting EKGs after starting patients on amitriptyline, with only 3 of the 6 tertiary centers doing the pre and post amitriptyline initiation EKGs. This practice variation likely exists due to paucity of data on the effect of low dose amitriptyline on cardiac conductance. Our study shows that post amitriptyline EKGs might not be necessary. The cost of performing an EKG as per CMS reimbursement schedule ranges from \$39-47. For every additional EKG there are additional intangible costs such as lost wages for parents, childcare costs for siblings, cost of transportation, etc. Performing unnecessary EKGs after initiating amitriptyline can add to the existing lofty healthcare expenditure in managing children with FGIDs, especially considering the high prevalence of chronic abdominal pain in school age children<sup>[1,27]</sup>.

The chronic use of TCAs in adult patients with chronic pain was not shown to result in clinically significant changes in cardiac conduction<sup>[28]</sup>. In our study ami-

triptyline use was associated with an increase in the heart rate and the QTc interval but none of these changes were significant enough to warrant discontinuation of amitriptyline. These findings suggest that once patients with FGIDs have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for reevaluation of cardiac conduction after starting low dose amitriptyline. Limitations of our study include the small sample size. Studies with larger sample size and longer duration are needed to confirm our findings and possibly influence future monitoring recommendations post initiation of TCA for FGID treatment. The findings might not be generalizable to other TCAs. The frequent use of TCAs other than amitriptyline for the treatment of FGIDs in children stress the importance of conducting similar studies with other TCAs<sup>[15]</sup>.

Our preliminary study suggests that amitriptyline used in low doses can be considered a relatively safe drug in the arsenal of pediatric gastroenterologists.

Our retrospective placebo controlled study suggests that the use of low dose amitriptyline in children with AP-FGIDs is probably not associated with clinically significant changes in cardiac conduction. A larger prospective study should be designed to confirm these findings.

## COMMENTS

### Background

Abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) commonly occur in childhood and adolescence. Low dose Amitriptyline is commonly used for off label treatment of AP-FGIDs in children although it has not been found to be better than placebo nor is it not approved for the treatment of FGIDs in children or adolescents. A dose-response association of tricyclic antidepressants has been demonstrated with QTc prolongation. There is limited data in the literature regarding the cardiac toxicity of low dose Amitriptyline in children.

### Research frontiers

Information on electrocardiogram (EKG) changes in children who are on low dose Amitriptyline for treatment of FGIDs is sparse. Authors present data for the first time, which examines the effect of low dose Amitriptyline on cardiac conduction.

### Innovations and breakthroughs

The study shows that the use of low dose amitriptyline in children with AP-FGIDs is not associated with clinically significant changes in cardiac conduction.

### Applications

Performing unnecessary EKGs after initiating amitriptyline can add to the exist-

ing lofty healthcare expenditure in managing children with FGIDs, especially considering the high prevalence of chronic abdominal pain in school age children. There is a lot of practice variation amongst physicians in ordering a post Amitriptyline initiation EKG. Their data has the potential to decrease healthcare expenditure and to reduce practice variation.

### Terminology

AP-FGIDs are among the most common medical afflictions in childhood and adolescence. The AP-FGIDs have been categorized by the Rome III criteria into irritable bowel syndrome (IBS), functional abdominal pain, functional dyspepsia and abdominal migraine.

### Peer review

The study was a secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating Amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and IBS according to the Rome II criteria. They aimed to better understand the effects of low dose Amitriptyline on cardiac conduction in children. They reviewed the EKG findings before and after initiation of Amitriptyline in a large multicenter study conducted by their group assessing the efficacy of Amitriptyline in children with AP-FGIDs. They found that none of the patients had any baseline EKG abnormality. None of the patients developed borderline QTc prolongation or LQTS after they were started on Amitriptyline. They conclude that the study findings suggest that once patients with FGIDs have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for reevaluation of cardiac conduction after starting low dose amitriptyline.

## REFERENCES

- 1 Saps M, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C. A prospective school-based study of abdominal pain and other common somatic complaints in children. *J Pediatr* 2009; **154**: 322-326 [PMID: 19038403 DOI: 10.1016/j.jpeds.2008.09.047]
- 2 Hyams JS, Burke G, Davis PM, Rzepski B, Andrulonis PA. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. *J Pediatr* 1996; **129**: 220-226 [PMID: 8765619]
- 3 Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75**: 234-241 [PMID: 15001975 DOI: 10.1016/j.clpt.2003.09.019]
- 4 Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. *Arch Gen Psychiatry* 2008; **65**: 94-101 [PMID: 18180433 DOI: 10.1001/archgenpsychiatry.2007.5]
- 5 Vahedi H, Merat S, Momtahan S, Kazzazi AS, Ghaffari N, Olfati G, Malekzadeh R. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2008; **27**: 678-684 [PMID: 18248658 DOI: 10.1111/j.1365-2036.2008.03633.x]
- 6 Talley NJ, Kellow JE, Boyce P, Tennant C, Huskic S, Jones M. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. *Dig Dis Sci* 2008; **53**: 108-115 [PMID: 17503182 DOI: 10.1007/s10620-007-9830-4]
- 7 Morgan V, Pickens D, Gautam S, Kessler R, Mertz H. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. *Gut* 2005; **54**: 601-607 [PMID: 15831901 DOI: 10.1136/gut.2004.047423]
- 8 Rajagopalan M, Kurian G, John J. Symptom relief with amitriptyline in the irritable bowel syndrome. *J Gastroenterol Hepatol* 1998; **13**: 738-741 [PMID: 9715427]
- 9 Greenbaum DS, Mayle JE, Vanegeren LE, Jerome JA, Mayor JW, Greenbaum RB, Matson RW, Stein GE, Dean HA, Halvorsen NA. Effects of desipramine on irritable bowel syndrome compared with atropine and placebo. *Dig Dis Sci* 1987; **32**: 257-266 [PMID: 3545719]
- 10 Tripathi BM, Misra NP, Gupta AK. Evaluation of tricyclic compound (trimipramine) vis-a-vis placebo in irritable bowel syndrome. (Double blind randomised study). *J Assoc Physicians India* 1983; **31**: 201-203 [PMID: 6358181]
- 11 Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. *World J Gastroenterol* 2009; **15**: 1548-1553 [PMID: 19340896]
- 12 Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. *Cochrane Database Syst Rev* 2011; : CD008013 [PMID: 21735420 DOI: 10.1002/14651858.CD008013.pub2]
- 13 Bahar RJ, Collins BS, Steinmetz B, Ament ME. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. *J Pediatr* 2008; **152**: 685-689 [PMID: 18410774 DOI: 10.1016/j.jpeds.2007.10.012]
- 14 Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, Di Lorenzo C. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology* 2009; **137**: 1261-1269 [PMID: 19596010 DOI: 10.1053/j.gastro.2009.06.060]
- 15 Teitelbaum JE, Arora R. Long-term efficacy of low-dose tricyclic antidepressants for children with functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2011; **53**: 260-264 [PMID: 21865971 DOI: 10.1097/MPG.0b013e318217df7c]
- 16 Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weillburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ* 2013; **346**: f288 [PMID: 23360890 DOI: 10.1136/bmj.f288]
- 17 James LP, Kearns GL. Cyclic antidepressant toxicity in children and adolescents. *J Clin Pharmacol* 1995; **35**: 343-350 [PMID: 7650221]
- 18 Thoa NM, Murray CD, Winchester WJ, Roy AJ, Pitcher MC, Kamm MA, Emmanuel AV. Amitriptyline modifies the visceral hypersensitivity response to acute stress in the irritable bowel syndrome. *Aliment Pharmacol Ther* 2009; **29**: 552-560 [PMID: 19076934 DOI: 10.1111/j.1365-2036.2008.03918.x]
- 19 Mertz H, Fass R, Kodner A, Yan-Go F, Fullerton S, Mayer EA. Effect of amitriptyline on symptoms, sleep, and visceral perception in patients with functional dyspepsia. *Am J Gastroenterol* 1998; **93**: 160-165 [PMID: 9468233 DOI: 10.1111/j.1572-0241.1998.00160.x]
- 20 Chopra N, Laver D, Davies SS, Knollmann BC. Amitriptyline activates cardiac ryanodine channels and causes spontaneous sarcoplasmic reticulum calcium release. *Mol Pharmacol* 2009; **75**: 183-195 [PMID: 18845675 DOI: 10.1124/mol.108.051490]
- 21 Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs* 2011; **25**: 473-490 [PMID: 21649448 DOI: 10.2165/11587800-000000000-00000]
- 22 Alvarez PA, Pahissa J. QT alterations in psychopharmacology: proven candidates and suspects. *Curr Drug Saf* 2010; **5**: 97-104 [PMID: 20210726]
- 23 Wilens TE, Biederman J, Baldessarini RJ, Geller B, Schleifer D, Spencer TJ, Birmaher B, Goldblatt A. Cardiovascular effects of therapeutic doses of tricyclic antidepressants in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 1491-1501 [PMID: 8936916]
- 24 Johnson A, Giuffre RM, O'Malley K. ECG changes in pediatric patients on tricyclic antidepressants, desipramine, and imipramine. *Can J Psychiatry* 1996; **41**: 102-106 [PMID: 8705955]
- 25 Patra KP, Sankararaman S, Jackson R, Hussain SZ. Significance of screening electrocardiogram before the initiation of amitriptyline therapy in children with functional abdominal pain. *Clin Pediatr (Phila)* 2012; **51**: 848-851 [PMID: 22619399 DOI: 10.1177/0009922812447890]

- 26 **Basavarajaiah S**, Wilson M, Whyte G, Shah A, Behr E, Sharma S. Prevalence and significance of an isolated long QT interval in elite athletes. *Eur Heart J* 2007; **28**: 2944-2949 [PMID: 17947213 DOI: 10.1093/eurheartj/ehm404]
- 27 **Dhroove G**, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? *J Pediatr Gastroenterol Nutr* 2010; **51**: 579-583 [PMID: 20706149 DOI: 10.1097/MPG.0b013e3181de0639]
- 28 **da Cunha RJ**, Barrucand L, Verçosa N. A study on electrocardiographic changes secondary to the use of tricyclic antidepressants in patients with chronic pain. *Rev Bras Anesthesiol* 2009; **59**: 46-55 [PMID: 19374215]

**P-Reviewer:** Bashashati M, Bhalla C, Magazzu G  
**S-Editor:** Ma YJ **L-Editor:** A **E-Editor:** Zhang DN





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045