Pharmacotherapy of Neurally Mediated Syncope

David G. Benditt, MD; Gerard J. Fahy, MD; Keith G. Lurie, MD; Scott Sakaguchi, MD; William Fabian, MD; Nemer Samniah, MD

Abstract—A wide variety of pharmacological agents are currently used for prevention of recurrent neurally mediated syncope, especially the vasovagal faint. None, however, have unequivocally proven long-term effectiveness based on adequate randomized clinical trials. At the present time, β-adrenergic receptor blockade, along with agents that increase central volume (eg, fludrocortisone, electrolyte-containing beverages), appear to be favored treatment options. The antiarrhythmic agent disopyramide and various serotonin reuptake blockers have also been reported to be beneficial. Finally, vasoconstrictor agents such as midodrine offer promise and remain the subject of clinical study. Ultimately, though, detailed study of the pathophysiology of these syncopal disorders and more aggressive pursuit of carefully designed placebo-controlled treatment studies are essential if pharmacological prevention of recurrent neurally mediated syncope is to be placed on a firm foundation. (Circulation. 1999;100:1242-1248.)

Key Words: syncope ■ nervous system ■ pharmacology ■ Cardiovascular Drugs

Neurally mediated (neurocardiogenic) syncope comprises a number of clinical conditions in which symptomatic systemic hypotension occurs as a result of a transient disturbance of neural reflex cardiovascular control (Table 1).1-3 The vasovagal faint, carotid sinus syndrome, and postmic-turition syncope are the most common forms of the neurally mediated faint. Others, including cough syncope and postex-ertional syncope, are less frequently encountered.

This communication focuses on the pharmacological op-tions that have been proposed for preventing neurally medi-ated faints, and especially the vasovagal faint, because it has been the most thoroughly studied. The objective is to provide an overview of the pharmacology and pertinent proposed modes of action of those agents that may be of benefit.

Drug Therapy of Neurally Mediated Syncope:

Basic Principles

Most individuals who experience a neurally mediated faint (particularly vasovagal fainters) require no additional therapy beyond education (ie, recognition of premonitory symptoms, avoidance of triggering events, and awareness of useful evasive actions) and reassurance regarding the non-life-threatening nature of the condition. On occasion, stress and anxiety management may be warranted. Various more aggressive nonpharmacological (eg, support hose, extended exposure to upright posture, pacemakers) and pharmacolog-ical treatment options are usually reserved for those relatively few individuals who experience frequent syncope and/or when symptoms cause excessive lifestyle difficulties, threaten employment, or result in unacceptable risk of physical injury to the patient or others.

Currently, drugs are used for both diagnostic and therapeutic purposes in the patient with neurally mediated syncope.1-3 In terms of diagnostic applications, agents such as isoproter-enol, edrophonium, nitroglycerin, and adenosine have been reported to be helpful during tilt-table testing (ie, so-called pharmacological provocation technique).4-8 ATP and adeno-sine have also been found to unmask susceptibility to neurally mediated paroxysmal AV block, one of the important electrocardiographic manifestations of cardioinhibitory neurally mediated syncope.9,10 In regard to treatment, drugs may be used for both emergent resuscitation of severely hypotensive and bradycardic victims (eg, dopamine, norepinephrine, anticholinergics), as well as for long-term prevention of syn-cope recurrences. The resuscitation role is a relatively rare occurrence, being perhaps most often encountered during the course of an acute inferior wall myocardial infarction complicated by triggering of the Bezold-Jarisch reflex. Long-term prophylaxis is a much more common issue; however, drug efficacy in this setting remains controversial, and certain important caveats need to be noted. First, to date, all evidence supporting the utility of prophylactic pharmacological inter-ventions in vasovagal syncope is undermined by absence of large-scale randomized controlled treatment trials. Virtually all existing published reports are uncontrolled. Second, for most of the proposed treatments, the overall published expe-rience is small and retrospective. Finally, the study end points have often been unrealistic. Specifically, it is unlikely that any tolerable intervention will entirely eliminate all events (a situation comparable, for example, to current treatment of paroxysmal atrial fibrillation). Moreover, because symptoms may wax and wane in frequency over many months, it is often difficult to assess the efficacy of any intervention. Conse-
TABLE 1. Neurally Mediated Syncopal Syndromes

<table>
<thead>
<tr>
<th>Vasovagal syncope (common or emotional faint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid sinus syncope</td>
</tr>
<tr>
<td>Postmicturition syncope</td>
</tr>
<tr>
<td>Airway stimulation</td>
</tr>
<tr>
<td>Cough syncope</td>
</tr>
<tr>
<td>Sneezing syncope</td>
</tr>
<tr>
<td>Gastrointestinal stimulation</td>
</tr>
<tr>
<td>Swallow syncope, defecation syncope</td>
</tr>
<tr>
<td>Raised intrathoracic pressure</td>
</tr>
<tr>
<td>Trumpet playing, weight lifting</td>
</tr>
<tr>
<td>Glossopharyngeal neuralgia</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Syncope associated with aortic stenosis</td>
</tr>
<tr>
<td>Syncope accompanying onset of certain tachyarrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia, and possibly certain episodes of ventricular tachycardia)</td>
</tr>
</tbody>
</table>

Beta-adrenergic action of epinephrine may facilitate peripheral vasodilatation.

Beta-Adrenergic blocking drugs have been evaluated during both acute intravenous drug administration and longer-term oral use in vasovagal fainters. For example, Asso et al.19 observed that in a cohort of 21 consecutive patients followed up for at least 3 years, 11 exhibited conversion of a positive tilt-table response to a negative response after parenteral administration of metoprolol (10 mg). During follow-up, only 1 of these metoprolol responders had a clear-cut syncopal episode. Metoprolol nonresponders were treated with alternative agents, and consequently the value of a tilt-test “failure” for predicting ineffective therapy was not evaluated. The latter question, however, was addressed in a study by Muller et al.20 In this report, metoprolol proved effective in preventing recurrences of syncope over a 10-month follow-up period in 7 of 12 patients who had had a negative tilt response after administration of intravenous metoprolol but also in 2 of 3 patients who had remained tilt-positive after parenteral drug. Muller et al. suggested that the apparent discordance between apparent failure during acute testing and subsequent long-term “success” may be attributable to pharmacokinetic factors. Parenteral metoprolol is lipid soluble and has a large volume of distribution. Therefore, the adequacy of tissue concentrations may be an issue after acute administration, with the preponderance of drug going to tissues with high blood flow and lipid content. Conversely, oral metoprolol undergoes a hepatic “first-pass” effect, which may lead to interindividual differences during oral treatment. Others argue that the findings simply point to the inadequacy of tilt-table testing for predicting treatment outcomes and/or the ineffectiveness of beta-adrenergic blockade in this setting. However, in contrast to the above-noted findings with parenteral metoprolol, Sra et al.21 found a strong concordance between the effects of intravenous esmolol during tilt-testing and subsequent beta-adrenergic blocker efficacy. In their report, esmolol eliminated susceptibility to tilt-induced syncope in 17 of 27 tilt-table–positive syncope patients, and in all 17 cases, subsequent oral beta-adrenergic blockade therapy with metoprolol was effective. They suggest that because esmolol administration is associated with stable plasma concentrations within 4 minutes and a rapid dose-dependent beta-adrenergic blockade is achieved and maintained, it provides a more consistent patient-to-patient beta-adrenergic blocking effect after acute administration than does metoprolol.

Metoprolol, pindolol, and atenolol have been the most frequently studied beta-adrenergic blockers in vasovagal syncope.4,19–25 Metoprolol was the first beta-blocker tested in tilt-induced syncope, on the bases of both its availability for parenteral testing in the United States and its relative cardioselectivity.4 Pindolol has gained favor because of its intrinsic sympathomimetic activity, which diminishes the severity of resting bradycardia in treated patients.22 Overall, there is as yet no compelling evidence to suggest that any beta-adrenergic blocker is superior to others.

Disopyramide

Disopyramide is a class 1a antiarrhythmic agent with prominent vagolytic side effects and a disconcerting degree of
negative inotropic effect. The latter attribute caused considerable concern regarding the usefulness of the drug in many antiarrhythmic applications but was paradoxically beneficial in patients with obstructive cardiomyopathy. On the basis of the latter observation, we proposed its use in preventing vasovagal syncope.27 The rationale at the time was that agents that diminish cardiac contractility might reduce stretch on cardiac and other centrally located cardiovascular receptors (e.g., aortic arch, pulmonary arteries) and thereby diminish afferent neural reflex traffic. In addition, the vagolytic action of disopyramide offered the opportunity for maintaining heart rate and possibly alleviating ancillary vagally mediated symptoms associated with vasovagal episodes. Potential adverse consequences included torsade de points ventricular tachycardia in patients prone to drug-induced QT interval prolongation, urinary tract obstruction in older patients, and glaucoma.

Disopyramide continues to be used in vasovagal syncope, although its utility has been questioned. Among 21 patients followed up by Morillo et al28 for an average of 30 months, syncope recurrence was comparable in both disopyramide-and placebo-treated groups (disopyramide, 27%; placebo, 30%). End points such as time to first recurrence or syncope burden were not reported. Other studies support the clinical utility of disopyramide phosphate. The required dose of disopyramide, however, has been a source of controversy, with the range varying from 200 to >700 mg/d. In this regard, Kelly et al29 pointed out that doses as high as 450 mg/d were ineffective in many of their patients and that the mean daily dose required for success was 700±219 mg in their 15 study patients. Additional placebo-controlled experience with disopyramide is needed. Currently, controversy regarding its effectiveness aside, disopyramide is best chosen for the young, active fainter without structural heart disease or QT-interval prolongation. In this setting, it may be more tolerable than a β-adrenergic blocker.

Serotonin Reuptake Blockers
Serotonin (5-hydroxytryptamine) is a neurotransmitter important in blood pressure regulation. Activation of cerebral serotonin receptors inhibits sympathetic nervous system activity and thereby facilitates a vasodepressor response. Although little is known regarding serotonin levels during neurally mediated fains, 2 indirect lines of evidence suggest at least the possibility of a contributory role. First, intracerebroventricular serotonin administration has been reported to inhibit sympathetic neural outflow in general while simultaneously increasing adren sympathetic stimulation. This finding could account for the combination of diminished peripheral vasoconstriction (reduced synaptic norepinephrine release) and concomitant excess epinephrine excretion known to occur in vasovagal fainters. Second, clinical observations suggest that serotonin reuptake blockers may diminish susceptibility to certain neurally mediated syncopal events. Selective serotonin reuptake blockers reversibly block serotonin reuptake in the synaptic cleft, ultimately reducing the effects of serotonin on sympathetic neural activity and thereby possibly moderating vasodepressor tendencies in neurally mediated syncope. In this regard, an early uncontrolled report examined the effects of fluoxetine hydrochloride in 16 patients who had failed conventional pharmacological approaches (scopolamine, disopyramide, etc). Thirteen of these 16 patients tolerated long-term therapy, and 7 (44%) remained syncope-free during 19±9 months of follow-up. Subsequently, the serotonin inhibitor sertraline hydrochloride was assessed in 17 patients; 3 were intolerant of therapy, and 5 remained tilt-table positive. Of the remaining tilt-table–negative patients, all were reported to have remained asymptomatic during 12±5 months of follow-up. Finally, Grubb and Kosinski90 suggest that the serotonin reuptake inhibitor verlafaxine hydrochloride may be even more effective. To date, however, all of these observations should be considered anecdotal.

Serotonin reuptake inhibitors may also be useful in forms of neurally mediated syncope other than vasovagal syncope. In carotid sinus syndrome, Grubb et al40 observed apparently beneficial effects of sertraline in one case and fluoxetine in another. These observations, if confirmed, may be important because, with the possible exception of midodrine, there are as yet no other pharmacological agents to assist in treating patients with nonvasovagal neurally mediated syncope.

Midodrine and Other Vasoconstrictors
Drugs that promote vasoconstriction (or at least impede vasodilatation associated with the vasodepressor component of neurally mediated syncope) are natural contenders for prophylactic treatment of the neurally mediated syncopal syndromes. In the past, ephedrine, dihydroergotamine, and etilephrine have been tried at various times. However, drug-induced hypertension, tachyphylaxis, and inconsistent effectiveness have largely eliminated their use. For instance, a multicenter randomized placebo-controlled study examining the utility of etilephrine (a relatively weak α- and β-adrenergic agonist) in neurally mediated syncope was terminated after no apparent etilephrine benefit was observed. Occurrence of syncope (etilephrine, 25.9%; control, 23.6%) and time to first syncope recurrence did not differ significantly between active drug–treated and placebo-treated patients. On the other hand, early experience with the recently introduced α1-agonist midodrine has been encouraging in both orthostatic hypotension and neurally mediated syncope applications.45–46

Midodrine [1(2′,5′-dimethoxyphenyl)-2-glycinamido-ethanol-HCl] produces both arteriolar constriction and diminished venous pooling.43,44 Midodrine is absorbed from the gastrointestinal tract and undergoes hepatic metabolism to an active metabolite, desglymidodrine. The latter reaches peak levels in ~40 minutes and induces arteriolar and venous capacitance constriction. Elimination is via the urine. The duration of action is 4 to 6 hours, thereby requiring 3 to 4 daily doses. The initial starting dose is 2.5 mg 3 times daily, with the maximum dose being in the range of 40 mg/d. Neither midodrine nor its desglymidodrine metabolite crosses the blood-brain barrier. They have minimal cerebral and cardiac effects. Scalp tingling is perhaps the most common and annoying side effect with this otherwise generally well-tolerated agent.
The effects of midodrine have been studied in greatest detail in patients with neurogenic orthostatic hypotension. Gilden et al reported observations of a dose-ranging placebo-controlled crossover trial in 97 individuals. An almost 30% average increase in standing systolic blood pressure was observed, with the dose of 10 mg 3 times daily seeming to be the most effective. More recently, Sra et al provided findings in 11 patients (average age, 34 years) with recurrent vasovagal syncope whose symptoms had not been adequately controlled on conventional medications. One patient did not tolerate the drug because of headache and the development of hypertension despite a relatively low midodrine dose (7.5 mg/d). Among the remainder, 5 were symptom-free during the average 17-week follow-up, whereas 4 others reported symptom improvement compared with the 3-month baseline period just before they entered the trial. In our recent experience with 20 patients who had recurrent syncope over an average of >5 years despite multiple treatment regimens (average of 2.3 drugs), 13 remained completely asymptomatic after 14 months on midodrine therapy (average daily dose, 22 mg).

Volume Maintenance
Maintenance of central volume is an underemphasized aspect of vasovagal syncope prevention, particularly in cases in which dehydration (eg, athletes) or extended periods of upright posture (eg, military) appear to play a role. In these circumstances, patients can be advised to liberalize their salt intake and use electrolyte-containing beverages (eg, sport drinks). The addition of fludrocortisone may also be beneficial. Fludrocortisone increases sodium and fluid retention and has been reported to sensitize α-adrenergic receptors (suggesting a possible synergism with midodrine). It is generally very well tolerated and is often used as a first choice in younger individuals without other cardiovascular disease.

Other Clinical Pharmacological Avenues
Other pharmacological agents have been reported to be helpful, but for the most part, the evidence is very limited. One such drug is theophylline, a commonly used bronchodilator with adenosine receptor blocking action as well as an element of sympathomimetic activity. In this regard, long-acting theophylline preparations were proposed for treatment of certain young patients with neurally mediated symptomatic bradycarrhythmias. A much more recent report describing the use of ATP and adenosine as provocative agents for identifying a subset of patients in whom paroxysmal AV block is a prominent manifestation of neurally mediated syncope has revived interest in theophylline and related adenosine A1-receptor blockers. As a rule, however, few patients with vasovagal syncope respond to theophylline alone. The same may be said of scopolamine, which until recently was available for convenient administration by transcutaneous skin patch (usually applied every other day). Apart from inconsistent efficacy, scopolamine therapy tended to be associated with frequent troublesome anticholinergic side effects as well as tachyphylaxis. Consequently, it was never a popular treatment choice. Finally, 1 study reported methylphenidate to be beneficial, but the clinical experience is far too limited to warrant further comment.

Potential Novel Pharmacological Approaches
Currently, our understanding of the factors that contribute to individual susceptibility to neurally mediated faints is very limited. Nevertheless, differences in neurohumoral and neurorereflex status appear to exist between individuals who are about to experience a vasovagal faint and those who are not. Examples of these include markedly elevated epinephrine, vasopressin, β-endorphins, and pancreatic polypeptide levels and altered baroreceptor sensitivity in the faint-prone individual. Such differences (among many others of which we are as yet unaware) may impact the capability of the central nervous system to protect circulatory stability. In this regard, β-endorphin levels are increased in both vasovagal syncope and the analogous second stage of hemorrhagic shock. The trigger for this increase and its precise timing are not known. However, as endorphin levels increase, their central action would be expected to accentuate efferent parasympathetic activity and possibly diminish efferent sympathetic activity. In an experimental hemorrhage model, intracisternal administration of the opioid receptor blocker naloxone was effective in preventing hypotension. However, this effect was not demonstrable with peripheral naloxone administration during study of neurally mediated syncope in humans. Possibly, then, endorphins may contribute to the evolving faint, and agents capable of blunting this effect may have therapeutic utility.

The possibility that nitric oxide may be a mediator in the vasodepressor response has been considered recently. Nitric oxide release from endothelial cells in the peripheral vasculature is known to contribute to smooth muscle relaxation. Nitric oxide is also known to play a role in the hypotension associated with sepsis. Experimental studies suggest that nitric oxide release may be a regulator of sympathetic neural tone and in addition, certain parasympathetic nerves terminating in the adventitia of large cerebral and retinal blood vessels are known to contain nitric oxide synthetase. In this regard, increased urinary cyclic 3′,5′-GMP (a presumed marker of nitric oxide activity) was reported during tilt-table testing. Furthermore, nitric oxide activity has been associated with the forearm vascular dilatation accompanying mental stress. On the other hand, Dietz et al did not observe reversal of forearm vascular dilatation with the nitric oxide synthetase inhibitor Nω-monomethyl-arginine (L-NMMA). Similarly, findings suggesting that vasovagal syncope is accompanied by cerebrovascular spasm are not easily reconciled with the nitric oxide hypothesis, given the known nitric oxide synthetase activity in cerebral vessels.

Role of Tilt-Table Testing in Assessing Drug Therapy
It is generally agreed that head-up tilt-table testing is an important diagnostic aid in the evaluation of patients with recurrent syncope of unknown origin. Conversely,
the value of tilt-table testing to qualify pharmacological agents for use in neurally mediated syncope patients or for predicting treatment efficacy in patients with neurally mediated vasovagal syncope is less certain. Table 2 summarizes findings from a number of published studies in which treatment for vasovagal syncope was based on findings during tilt-table testing studies but in which subsequent effectiveness was determined by clinical follow-up. In brief, ≈90% of patients in whom therapy resulted in a negative tilt study remained syncope-free during the observation period (mean, 18.5 months), a finding suggesting the utility of a tilt-table–guided approach. However, this outcome must be interpreted cautiously, given the absence of either placebo controls or a measure of the effect of empirical therapy in most studies. With regard to placebo control, the few available reports have usually failed to find benefit with current therapies. To date, only atenolol has been shown to be effective in a randomized controlled trial. The latter observation tends to support the utility of tilt-table testing for evaluating treatment options (particularly drugs), but larger prospective trials are still needed.

Conclusions

In conclusion, a wide variety of pharmacological agents are used to treat neurally mediated syncope. None, however, have unequivocally proven long-term effectiveness as shown by randomized clinical trials. Nevertheless, β-adrenergic receptor blockade and agents that increase central volume (eg, fludrocortisone; electrolyte-containing beverages), currently appear to be favored treatment options. Disopyramide and various serotonin reuptake blockers are also reported to be beneficial. Finally, vasoconstrictors such as midodrine offer promise, assuming that tachyphylaxis (a common problem with this class of drugs) does not hamper their continued effectiveness. Ultimately, however, more intensive study of the pathophysiology of these syncopal disorders and more aggressive pursuit of carefully designed placebo-controlled treatment studies are essential if pharmacological prevention of recurrent neurally mediated syncope is to be placed on a firm foundation.

Acknowledgments

The authors would like to thank Barry L.S. Detloff and Wendy Markuson for assistance in preparation of the manuscript.

References


### TABLE 2. Tilt-Table Testing for Predicting Effectiveness of Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tilt-Negative on Proposed Treatment</th>
<th>Follow-Up, mo</th>
<th>No Syncope During Follow-Up, %</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubb et al(^{20})</td>
<td>15</td>
<td>16</td>
<td>14 (93)</td>
<td>B-blk, Scop, Diso, Flcr</td>
</tr>
<tr>
<td>Sra et al(^{21})</td>
<td>34</td>
<td>18</td>
<td>32 (94)</td>
<td>B-blk, Diso</td>
</tr>
<tr>
<td>Grubb et al(^{27})</td>
<td>10</td>
<td>21±2</td>
<td>10 (100)</td>
<td>B-blk, Scop, Diso, Pacer</td>
</tr>
<tr>
<td>Sra et al(^{23})</td>
<td>19</td>
<td>16</td>
<td>18 (94)</td>
<td>B-blk, Diso, Theo</td>
</tr>
<tr>
<td>Miletstein et al(^{27})</td>
<td>10</td>
<td>20±5</td>
<td>9 (90)</td>
<td>Diso</td>
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<tr>
<td>Raviele et al(^{46})</td>
<td>7</td>
<td>12 (9–16)</td>
<td>6 (86)</td>
<td>Etillep, Scop</td>
</tr>
<tr>
<td>Brigone et al(^{24})</td>
<td>15</td>
<td>11±7</td>
<td>7 (46)</td>
<td>B-blk, Ergot, others</td>
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<tr>
<td>Asso et al(^{19})</td>
<td>11</td>
<td>13 (1–36)</td>
<td>9 (82)</td>
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<td>Lurie et al(^{22})</td>
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<td>19±0.9</td>
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<td>14</td>
<td>24±11</td>
<td>14 (100)</td>
<td>B-blk, Scop, Diso, B-blk+Flcr</td>
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<tr>
<td>Grubb et al(^{27})</td>
<td>17</td>
<td>23±7</td>
<td>17 (100)</td>
<td>Flcr, B-blk, Diso</td>
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<tr>
<td>Strieper et al(^{46})</td>
<td>16</td>
<td>11.7 (6–14)</td>
<td>15 (94)</td>
<td>Pseudoephedrine</td>
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<tr>
<td>Cox et al(^{30})</td>
<td>118</td>
<td>28±11</td>
<td>106 (90)</td>
<td>B-blk</td>
</tr>
<tr>
<td>Muller et al(^{20})</td>
<td>12</td>
<td>10</td>
<td>7 (58)</td>
<td>B-blk</td>
</tr>
<tr>
<td>Natale et al(^{22})</td>
<td>210</td>
<td>34±22</td>
<td>198 (94)</td>
<td>B-blk, Diso, Theo, Ephed</td>
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<tr>
<td>Total</td>
<td>525</td>
<td>18.5</td>
<td>478 (91)</td>
<td></td>
</tr>
</tbody>
</table>

B-blk indicates β-adrenergic blockade; Scop, scopolamine; Diso, disopyramide; Flcr, fludrocortisone; Pacer, pacemaker; Theo, theophylline; Etillep, etilephrine; Ergot, ergotamine; and Ephed, ephedrine.


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Circulation. 1999;100:1242-1248
doi: 10.1161/01.CIR.100.11.1242
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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