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Vol. 41, Issue 7, April 15, 2019
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SHORT REPORT

Behavioral Interventions in Adults for Weight Loss or Weight Loss Maintenance

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: The U.S. Preventive Services Task Force evaluated the risks and benefits of interventions for weight loss and weight loss maintenance to prevent complications from obesity. Panelists found a moderate net benefit from weight loss-intensive behavioral interventions.

SOURCE: US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, et al. Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2018;320: 1163-1171.

Obesity is a serious and growing problem that affects more than one-third of U.S. adults. Health problems related to obesity are numerous. Obesity increases the risk and complications from disorders such as cardiovascular disease, endocrine problems, maladies of the musculoskeletal system, and specific carcinomas, and increases the risk for death.[1,2]

The U.S. Preventive Services Task Force (USPSTF) generates recommendations based on evaluation of evidence by a volunteer panel composed of experts in preventive medicine and primary care. Recommendations are based solely on peer-reviewed studies; neither cost nor accessibility is factored into the analysis. However, insurers often use these recommendations to determine coverage. Each recommendation receives a letter grade (A, B, C, D, or I) reflecting strength of evidence and any concerns about harm. The goal is to provide primary care providers and patients a platform for discussion regarding specific preventive measures.[3]

This article reflects the latest USPSTF recommendations regarding prevention of morbidity and mortality related to obesity in adults. The recommendation to offer or refer patients with a body mass index (BMI) of ≥ 30 kg/m2 for behavioral interventions received a "B" from the organization, meaning there is "moderate

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott, Acadia, Allergan, AstraZeneca, Avadel, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mylan, and Salix; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Executive Editor Leslie Coplin; Accreditations Manager Amy M. Johnson, MSN, RN, CPN; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

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Internal Medicine Alert (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

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certainty" that the net benefit is moderate. The USPSTF categorizes BMI from 25 to 29.9 kg/m^2 as overweight and BMI of ≥ 30 kg/m^2 as obese. BMIs higher than this are subdivided further into obesity classes 1, 2, and 3.[4]

The USPSTF evaluated studies related to behavioral or pharmaceutical interventions for weight loss or weight loss maintenance. It reviewed 124 studies: 80 involved behavioral-based weight loss; nine concerned behavior-based weight loss maintenance; 32 were about pharmacotherapy for weight loss; and three involved pharmacotherapy for weight loss maintenance. No surgical or weight loss device studies or trials were considered, as these were believed to fall outside the scope of the review.

The behavioral interventions consisted of a multimodal approach incorporating diet, physical activity, and psychological interventions in most reviewed studies. Most studies were intensive and included at least 12 sessions during year 1. Interventions ranged from in-person counseling sessions to DVD learning to text messaging. Participation rates were high. The degree of heterogeneity precluded a recommendation regarding the most effective type of behavioral intervention. However, these methods showed evidence of efficacy, with a risk ratio at 12- to 18-month follow-up of 1.94 (95% confidence interval, 1.70-2.22) for participants losing or maintaining at least 5% of baseline weight compared with control subjects. In other words, the behavioral intervention was associated with almost two times the probability of weight loss or weight loss maintenance in follow-up.

Pharmacotherapy investigations included the following agents usually combined with behavioral interventions: liraglutide (four trials), lorcaserin (four trials), naltrexone/bupropion (four trials), orlistat (21 trials), and phentermine/topiramate (three trials). The USPSTF found the pharmacotherapy trials to be of fair quality, but was unable to complete a meta-analysis because of high variability in outcome measures in the context of the limited number of studies for each agent. Additionally, it noted that fairly stringent criteria for inclusion in these trials (typically, participants needed to demonstrate medication compliance and/or meet a weight loss goal for eligibility) impeded the ability to generalize results. Potential harms of these agents may have led to an observed higher dropout rate when compared to the group with behavioral interventions only. However, those who completed the combined interventions lost more weight over 12 to 18 months than the group with behavioral interventions alone.

Given concerns about generalizability of the pharmacology studies, the potential harms, and the difficulty performing a meta-analysis, the USPSTF recommendations focused on multimodal intensive behavioral interventions and made no recommendations regarding psychopharmacological interventions.

Recommendations to offer or refer all adults with BMI ≥ 30 kg/m^2 to intensive, multicomponent behavioral interventions for weight loss or weight loss maintenance are clear. It is less clear how to convert the recommendations into a meaningful, clinically relevant process. In a November 2018 *JAMA* editorial, Haire-Joshu and Hill-Briggs noted barriers and challenges to making the recommendations reality. These include underdiagnosis of obesity in primary care, a decrease in weight management counseling over the last decade, and many higher-risk patients (young adults and those with lower socioeconomic status) who are less likely to see a primary care provider. Haire-Joshu and Hill-Briggs discussed the benefits of recruiting and training lay-persons to reach deep into communities rather than waiting for members of high-risk populations to come to primary care. They also discussed the advantages of training lifestyle or health coaches for this work.[5]

Although the USPSTF recommendations for intensive multimodal behavioral interventions were not specific, they do give rise to a few guidelines for patients. Most interventions included at least 12 sessions the first year. Most incorporated support for dietary modification along with physical activity. Primary care and integrative medicine providers remain at the forefront in screening, diagnosing, and referring patients with obesity. However, not all persons who are interested in weight loss seek medical care. Collaborating with well-trained community members to extend preventive efforts into areas traditionally not associated with medicine, such as

community centers, schools, and religious organizations, potentially can help providers reach this segment of the population. Public speaking and efforts at forming nutritionally sound public policy measures also can be effective ways to extend this message. These steps out of the office can help USPSTF recommendations become a reality for individuals who may not yet be part of a primary care practice. ■

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ABSTRACT & COMMENTARY

Medication First? Ablation First? Either Way, Make Weight Loss a Priority

By Joshua D. Moss, MD

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Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

SYNOPSIS: Weight loss management and aggressive risk factor modification associated with slowing or even reversal of atrial fibrillation progression.

SOURCE: Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: The REVERSE-AF study. *Europace* 2018;20:1929-1935.

Atrial fibrillation (AF) is known to be a progressive disease, often starting as paroxysmal episodes that become increasingly frequent and/or sustained, then evolving into persistent, long-standing persistent, and "permanent" forms. Prior research has clearly shown lower AF burden and fewer symptoms with sustained weight loss, as well as fewer episodes of new onset AF after bariatric surgery. Middeldorp et al sought to characterize the impact of weight loss and risk factor management on progression (or regression) of AF.

Data from the previously published LEGACY study cohort[1] were analyzed retrospectively. Of 825 patients with symptomatic AF and BMI > 27 kg/m^2 referred to a single center in Australia, 355 patients who had not undergone AF ablation and who had at least 24 months of follow-up were included in the final cohort. Other exclusion criteria were terminal cancer, severe medical illness, or permanent AF. Patients participated in a dedicated physician-led clinic focused on weight loss and risk factor modification, with a structured program that included one-on-one individualized counseling. Goals included an initial target of > 10% weight loss, resting home blood pressures < 130/80 mmHg on at least 80% of readings, cholesterol and glucose intolerance management (with lifestyle measures and pharmacotherapy as needed), treatment of sleep apnea, smoking cessation, and alcohol reduction. Patients were seen in a separate dedicated AF clinic for arrhythmia management, with rate and rhythm control tactics at the discretion of the treating physician.

For outcomes analysis, the 355 patients in the final cohort were divided by the extent of weight loss achieved: < 3% (group 1 = 116 patients), 3-9% (group 2 = 104 patients), and ≥ 10% (group 3 = 135 patients). Baseline characteristics of the three groups were similar, with mean BMI around 33 kg/m^2, although group 3 patients were slightly older (mean age, 65 years vs. 63 years in group 2 and 61 years in group 1). All groups were followed for a mean of about four years. The type of AF and burden for each patient were assessed with at least annual clinical review, 12-lead ECG, device interrogation, and seven-day Holter monitoring.

After controlling for a multitude of risk factors, the extent of weight loss achieved was significantly associated with AF progression. More than 40% of patients in group 1 (with < 3% weight loss) saw progression of their AF from paroxysmal to persistent. Only 25% were free of AF at final follow-up; most of the remaining patients saw no change. In marked contrast, 36% of patients in group 3 (with ≥ 10% weight loss) showed reversal of AF from persistent to paroxysmal, and 52%

were free of AF over the final year of follow-up; only 3% of patients progressed and 9% showed no change. All groups lowered antiarrhythmic drug use rates by the end of follow-up, with the greatest change by far in group 3. Other notable findings associated with greater weight loss in group 3 were a reduction in AF burden (including 85% of patients with paroxysmal episodes lasting two to seven days initially, regressing to ≤ 48-hour episodes) and lower mean systolic blood pressure readings and less use of antihypertensive medications compared to groups 1 and 2.

■ COMMENTARY

The importance of focused weight loss efforts and risk factor modification in the prevention of AF has become increasingly clear. These data add dramatic new evidence to support such treatment to prevent disease progression. Eighty-eight percent of overweight patients who achieved ≥ 10% weight loss via a goal-directed, motivational, structured program with one-on-one individualized counseling experienced either a regression of their disease from persistent to paroxysmal or were free of AF at follow-up.

The primary limitation of the study is its observational nature, with all the biases inherent in the absence of randomization and prospective evaluation. Patients who can lose weight more easily also may be less likely to have progressive disease or perhaps had been overweight for a shorter period and had less attendant atrial remodeling. A direct causative effect of weight loss on AF regression cannot be inferred; still, the association is striking. The primary difficulty in applying the results of the study to clinical practice is actually achieving the kind of weight loss results seen in this single center's dedicated clinic. Busy clinicians are unlikely to have time to provide comparable, individualized weight loss and risk factor management. However, a strong argument could be made in investing in such a dedicated stand-alone clinic, as long-term healthcare costs undoubtedly would be lower. Data on ablation procedures from this study serve as a good example. More patients in group 3 were arrhythmia-free at the time of final follow-up than patients who were arrhythmia-free in groups 1 and 2 combined, and most were without ablation. Arrhythmia-free patients in group 1 most often required multiple ablations, while those in group 2 most often required one ablation.

Clinicians will continue to offer patients all options for management of AF, including rate-control (if appropriate and effective at mitigating symptoms), antiarrhythmic drug therapy, and ablation. Some electrophysiologists defer offering a first ablation procedure until a certain goal weight is achieved, both to minimize procedural risks and maximize chances for long-term success. No matter what route is chosen, aggressive weight loss efforts and risk factor modification for overweight patients undoubtedly should be a principle component of the treatment plan. ■

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ABSTRACT & COMMENTARY

Witness Observations in Diagnosing Transient Loss of Consciousness

By Louise M. Klebanoff, MD

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Dr. Klebanoff reports no financial relationships relevant to this field of study.

SYNOPSIS: Investigators found that adding witness-reported observations to patient demographics and patient-reported symptoms improved the diagnostic accuracy between epilepsy, syncope, and psychogenic nonepileptic seizures.

SOURCE: Chen M, Jamnadas-Khoda J, Broadhurst M, et al. Value of witness observations in the differential diagnosis of transient loss of consciousness. *Neurology* 2019;92:e895-e904.

The differential diagnosis of transient loss of consciousness (TLOC) includes epilepsy, syncope, and psychogenic nonepileptic seizures (PNES). The gold standard for confirming the diagnosis is simultaneously recording clinical events and physiological measures. In practice, this standard is reached rarely, and the diagnosis is made based on the patient's history and witnessed descriptions. Misdiagnosis rates of 25% have been reported. Chen et al performed a retrospective study evaluating the contribution of additional witness observations in determining the etiology of transient loss of consciousness. Previously, the authors demonstrated

that self-reportable associated symptoms collected using the Paroxysmal Event Profile (PEP), an 86-item symptom questionnaire, made an important diagnostic contribution in distinguishing between epilepsy, syncope, and PNES in laboratory-proven cases. When PEP data were added to basic patient information, 66% of patients with epilepsy, 91% with syncope, and 78% with PNES were classified correctly. The authors investigated to what extent a 31-item profile (Paroxysmal Event Observer [PEO]) of observer-reportable event manifestations improved the diagnostic differential.

The authors reviewed 249 patients from a total sample of 300 patients from three British medical centers who had completed both the PEP and PEO questionnaires (86 with epilepsy, 84 with syncope, and 79 with PNES). All diagnoses were confirmed by recordings of typical events with video electroencephalogram (EEG), ambulatory EEG, or tilt-table. Of 31 items collected, 24 differed significantly between the three groups. These factors were combined into four broader categories: unconsciousness, reduced self-control, excessive movement, and skin/face/recovery.

Observer-reported factors differentiated syncope and epilepsy better than patient-reported factors (accuracy: 96% vs. 85%; C-index $P = 0.0004$). When the analysis of the patient information was combined with that from observers, this distinction rose from 90% to 100% (C-index $P = 0.005$). In the differentiation of PNES and epilepsy, additional observer-reported factors improved the predictive accuracy from 76% to 83% (C-index $P = 0.006$) and from 93% to 95% (C-index $P = 0.098$) in PNES and syncope. When analyzed in isolation, more patients were classified correctly by the observer-derived data than by the patient-provided symptoms.

In this study, witness questionnaire responses correctly classified patients with a sensitivity of 84.4% and a specificity of 84.2%. The answers to the PEO factor "reduced self-control" distinguished most clearly among the three diagnostic groups, with low levels of TLOC-associated self-control more frequently observed in epilepsy than in syncope or PNES. Other distinguishing factors included that, unlike syncope and PNES, epileptic seizures "never" looked like normal sleep, and pale skin and limp collapse were more commonly seen in syncope than in epilepsy. PNES observers more commonly replied that they could "never" do something to make the attack pass more quickly. This study provides confirmatory data that witness-provided information contributes to the correct differentiation between epilepsy, syncope, and PNES. The witness-provided data were most useful in correctly distinguishing epilepsy from syncope or PNES. The differentiation of syncope from PNES was highly accurate without the addition of observation data. The poorest differentiation was between epilepsy and PNES. Although observer-provided data improved diagnostic accuracy, additional data (such as video EEG monitoring) likely will be required to optimize this differential.

■ COMMENTARY

This study provides support for the importance of witness observations in distinguishing common causes of transient loss of consciousness. By adding witness-reported observations to patient demographics and patient-reported symptoms, the diagnostic accuracy between epilepsy, syncope, and PNES improves. Although differentiating between epilepsy and PNES still may require additional data (such as a spell captured on video EEG), observer-reported data can improve the diagnostic accuracy of syncope and epilepsy significantly. Structured witness interviews that include observations of reduced self-control, sleep-like appearance, skin pallor, and/or limp limbs provide the most important distinguishing factors. ■

PHARMACOLOGY UPDATE

Esketamine Nasal Spray (Spravato) CIII

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a nasal spray for treatment-resistant depression (TRD). Esketamine is the S-enantiomer of racemic ketamine, which has been approved for parenteral use as induction and maintenance of general anesthesia since 1970. Parenteral ketamine also has been used off-label to treat severe depression. Esketamine nasal spray was granted breakthrough therapy and fast-track designations. It will be available as Spravato under a Risk Evaluation and Mitigation Strategy.

INDICATIONS

Esketamine, in conjunction with an oral antidepressant, is indicated for the amelioration of TRD in adults.[1]

DOSAGE

The recommended dose for the induction phase is 56 mg (one spray in each nostril) on day 1.[1] From week 1 to week 4, the dose is given twice per week (56 mg or 84 mg). For the maintenance phase (weeks 5-8), the dose is administered once weekly. For week 9 and beyond, the administration is every two weeks or once weekly. Dosage adjustment should be made based on efficacy and tolerability. Therapeutic benefits should be evaluated at the end of the induction phase to determine if treatment should continue. The dose should be administered under supervision of a healthcare provider in a certified healthcare setting. Blood pressure should be assessed before and after administration. The patient should be monitored for at least two hours after the self-administered dose and should be discharged only if he or she is clinically stable. Esketamine is available as a 56 mg dose kit that contains two 28 mg nasal spray devices and as an 84 mg dose kit that contains three 28 mg nasal spray devices.

POTENTIAL ADVANTAGES

Esketamine provides a new treatment option with a rapid onset of action for patients with TRD.

POTENTIAL DISADVANTAGES

Esketamine increases blood pressure and impairs attention, judgment, thinking, reaction speed, and motor skills.[1] The most common adverse reactions are dissociation, dizziness, sedation, vertigo, hypoesthesia, anxiety, lethargy, vomiting, and feeling drunk. Approximately 8-17% of those who use the nasal spray (vs. 1-3% who took placebo) showed an increase in systolic blood pressure of 40 mmHg and/or an increase in diastolic blood pressure of 25 mmHg within the first 1.5 hours after administration at least once during the first four weeks of treatment. Patients with hypertension or pre-existing aneurysmal vascular disorders may be at a higher risk for adverse cardiovascular or cerebrovascular effects.

Between 61% and 75% of treated patients developed dissociation or perceptual changes, derealization, and depersonalization. Esketamine may cause fetal harm.[1] Pregnancy planning and prevention should be considered in women of reproductive age. Patients should not drive until the next day after administration and after a restful sleep.[1] Long-term safety (e.g., psychotomimetic and dissociation reactions) and effectiveness have not been established. Esketamine may be abused or diverted and has been used recreationally. It is a Schedule III controlled substance.

COMMENTS

Esketamine is an N-methyl-D-aspartate (NMDA) receptor blocker, although it is unclear if this is the primary mechanism of action.[2] The efficacy was evaluated in three short-term studies and one long-term trial.[3] Only one of the short-term studies met the criteria for effectiveness.[1,3,4] Participants reported TRD and had not responded adequately to at least two different antidepressants with adequate dose and duration.[1] Subjects discontinued prior therapy and were randomized to twice-weekly doses of intranasal esketamine (56 mg or 84 mg; n = 114) or intranasal placebo (n = 109). All subjects were started on a new oral antidepressant (duloxetine, escitalopram, sertraline, or extended-release venlafaxine) at the judgment of the investigators. The primary efficacy endpoint was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the four-week, double-blind induction phase. MADRS is a 10-item, clinician-rated scale that ranges from 0 to 60.

Esketamine produced a mean difference of -4 over placebo (53% reduction vs. 42.3% from baseline scores of 37 and 37.3, respectively). Benefit was observed at 24 hours and maintained to day 28. At day 28, 67% of subjects received 84 mg twice daily. In the longer-term study, subjects who were in stable remission or stable responders were treated for 16 weeks with esketamine and an oral antidepressant.[1,5] Then, they were randomized to continue esketamine or intranasal placebo. The primary endpoint was time to relapse (defined as MADRS total score of ≥ 22 for two consecutive weeks), hospitalization for worsening depression, or other clinical indications of relapse. Subjects in the stable remission and stable responders groups showed significant delay in time to relapse compared to subjects taking placebo. IV ketamine (0.5 mg/kg) was compared to midazolam (0.02 mg/kg) in patients with major depression and a score ≥ 4 on the Scale for Suicidal Ideation (SSI).[6] A reduction of SSI score was 4.96 greater after ketamine than with midazolam at day 1. Fifty-five percent were responders (≥ 50% reduction in SSI) compared to 30% for midazolam.

CLINICAL IMPLICATIONS

The generally accepted definition for TRD is a minimum of two prior treatment failures and confirmation of prior adequate dose and duration.[7] Pharmacologic options for TRD have included augmentation, combination, and switching to another antidepressant.[8] Esketamine is a rapid-acting antidepressant with possible antisuicidal effect. However, long-term effectiveness and safety, including abuse and misuse potential, remains to be established. The cost will be between $590 and $885 per treatment session, with the initial month of therapy costing between $4,700 and $6,785. Subsequent weeks will cost about half as much (not including physician and office fees). ■

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CME QUESTIONS

1. **The USPSTF issued recommendations for interventions for weight loss and weight loss maintenance for adults with a body mass index ≥ 30 kg/m². Which of the following is true regarding this published report?**
   a. Behavioral interventions (multicomponent and intensive) are mostly cost effective and show greater net benefit and longevity of response when compared with surgical and pharmacotherapy interventions.
   b. Behavioral interventions (multicomponent and intensive) are associated with a net moderate benefit and are 25-30% safer than surgical procedures and about 15% safer than pharmacotherapy; the cost of behavioral interventions varies regionally and with type.
   c. Behavioral interventions (multicomponent and intensive) show a net moderate benefit with a grade B when all evidence is weighed, including potential of harm.
   d. Behavioral interventions (multicomponent and intensive) show a net moderate benefit with a grade B, and psychopharmacology interventions rank just behind with a grade C.

2. **In overweight patients with atrial fibrillation, what percent reduction in weight is associated with fewer atrial fibrillation events?**
   a. 3%
   b. 5%
   c. 7%
   d. 10%

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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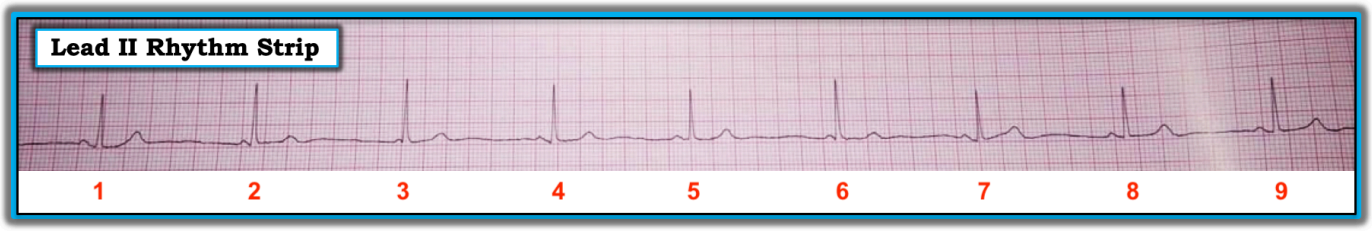
Dr. Grauer reports no financial relationships relevant to this field of study.

Is There AV Block?

The long lead II rhythm strip in the figure below was recorded at the standard 25 mm/second speed. This tracing was obtained from a middle-aged woman who presented to an outpatient clinic with noncardiac chest pain. How would one interpret this rhythm? Are there signs of AV block? Is it apparent if there is a cardiac problem?



The QRS complex is narrow in this single monitoring lead. The rhythm appears to be supraventricular. The rhythm is almost (but not completely) regular. P waves are present, but the PR interval does not remain constant throughout the tracing. When confronted with a difficult-to-interpret arrhythmia, it may be easiest to start with what one knows. In this case, the PR interval preceding beat 3 is too short to conduct. The PR interval preceding beats 2 and 6 also appears to be too short to conduct.

Is there an underlying sinus rhythm? Note that the PR interval preceding all other beats on this tracing (i.e., the PR interval before beats 1, 4-5, and 7-9) is longer than the PR interval preceding beats 2, 3, and 6.

Since the PR interval is equal and normal (~0.14/second) preceding beats 1, 4-5, and 7-9, and since P waves all are upright in this lead II monitoring strip, the underlying rhythm is sinus arrhythmia, with an overall ventricular rate less than 50 beats/minute.

Because the three beats that are preceded by a PR interval too short to conduct all feature a narrow QRS complex, and all look similar in morphology to the six sinus-conducted beats on this tracing, these three beats (i.e., beats 2, 3, and 6) must be junctional escape beats. Although the R-R interval varies slightly during this rhythm strip, the R-R interval preceding each of these three junctional beats is identical (6.6 large boxes in duration). This corresponds to a junctional escape rate of ~45 beats/minute.

The underlying rhythm is sinus bradycardia and arrhythmia. When the SA node slows to a rate below 45 beats/minute, the junctional escape rhythm takes over. When this happens, there is transient AV dissociation until the sinus rate speeds up to more than 45 beats/minute. A helpful clue that P waves are conducting again is when the R-R interval shortens. Thus, beats 4 and 5 are sinus-conducted beats. After junctional beat 6, the R-R interval again shortens, with resumption of sinus-conducted P waves for beats 7, 8, and 9.

There is no evidence of AV block on this tracing. There never are P waves that fail to conduct when given a chance to do so (i.e., the P waves just before beats 2, 3, and 6 never have a chance to conduct because the PR interval is just too short). Clinically, without more information (and a longer period of monitoring), there is no way to know whether the rhythm in the figure is pathologic. This could be a normal physiologic response if the patient was a healthy, endurance athlete with a baseline rhythm of sinus bradycardia. On the other hand, it could be a pathologic rhythm if this patient had sick sinus syndrome.

For more information about and further discussion on this case, please visit: https://bit.ly/2Joo2Vs.