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Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

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ABSTRACT & COMMENTARY

Putting the Genie Back in the Prescription Bottle

By Allan J. Wilke, MD

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

SYNOPSIS: Researchers recently developed an evidence-based algorithm for reducing the use of proton pump inhibitors.

SOURCE: Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-364.

Proton pump inhibitors (PPIs) are wonder drugs that have revolutionized our treatment of heartburn, esophagitis, gastric inflammation, and ulcer disease, making them among the most commonly prescribed medications in the United States. In 2015, esomeprazole (Nexium) was the fourth most commonly prescribed drug by number of monthly prescriptions with 15.2 million.[1] A study from 2006 found that in the United States, more than $10 billion is spent annually on this class of medication,[2] and it is safe to assume that we spend much more a decade later. The most common indications are heartburn and gastroesophageal reflux disease (GERD), and the recommended duration of treatment is four to eight weeks. A recommendation from the American Gastroenterological Association (AGA) states, "For pharmacological treatment of patients with [GERD], long-term acid suppression therapy ([PPIs] or histamine-2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals. The main identifiable risk associated with reducing or discontinuing acid suppression therapy is an increased symptom burden. It follows that the decision regarding the need for (and dosage of) maintenance therapy is driven by the impact of those residual symptoms on the patient's quality of life rather than as a disease control measure."[3] Although generally

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considered safe, PPIs can produce many adverse side effects, including, but not limited to, fractures, hypomagnesemia, *Clostridium difficile* infection, diarrhea, vitamin B12 deficiency, pancreatitis, and blood dyscrasias. These adverse effects are worse in the elderly, who can experience difficulties metabolizing and eliminating medications.[4] There are many reasons to stop PPIs beyond their possible adverse effects and expense. Polypharmacy, especially in the elderly, can lead to nonadherence, medication errors, and drug interactions. There is mounting evidence of their overuse.[5] However, PPIs are notoriously difficult to stop once started.

An interdisciplinary group from Canada, comprised of family physicians, a gastroenterologist, pharmacists, a methodologist, pharmacy residents, project coordinators, a librarian, and a master's student, described their method for devising a guideline to stop or reduce use of PPIs. The group chose to focus on adults taking PPIs for longer than 28 days to treat GERD or esophagitis; they excluded patients with Barrett's esophagus, severe esophagitis, or a history of bleeding gastrointestinal ulcers. Using a previously published method for guideline development, they followed a checklist and reviewed the literature for articles that addressed stopping or reducing the dose of PPIs — or as they termed it, "deprescribing."

Deprescribing can take several forms. First is "stopping," either immediately or with a defined taper. Then there is "stepping down," which is similar to stopping, except it is followed by a prescription for a histamine-2 receptor antagonist (H2RA). Finally, there is "reducing," which includes either "on-demand use" (stopping use completely when symptoms resolve and then restarting, if symptoms return) and "lower dose" (reducing to a maintenance dose after symptoms resolve).

Their systematic review yielded several findings, which guided the decision tree. Asymptomatic patients who reduced their dose of a PPI were no more likely to relapse than patients who continued with the standard dose. On-demand use and stepping down increased the risk of relapse compared to lower dose, but had the benefit of a lower pill burden and cost.

Their algorithm, conveniently published in a flow chart, starts with a basic but important question: "Why is patient taking a PPI?" It includes exclusion criteria for patients who should continue PPIs, recommendations for monitoring and follow-up, and advice on nonpharmacological approaches to treat heartburn and GERD.

■ COMMENTARY

This article is important because, although the overuse of PPIs is well documented, we haven't seen evidence-based advice on how to reverse it. As with every guideline, this one must be applied to the patient in front of you, and application should incorporate the patient's goals of care. The Choosing Wisely campaign, an initiative created by the American Board of Internal Medicine Foundation, offers a patient handout developed by Consumer Reports and the American Gastroenterological Association to help clinicians educate patients about treating heartburn and GERD.[6]

As good as this is, it is not enough. Similar to the strategy for decreasing our country's cesarean delivery rate, "don't do the first one," we need to think twice before we write the first PPI prescription. Have we recommended lifestyle changes (i.e., don't eat two to three hours before bed, raise the head of the bed, lose weight, and avoid dietary triggers) as the first step? Patients and clinicians may view taking a pill as the path of least resistance, but once down that path, it is difficult to get back to where we once belonged.

The authors host a website devoted to deprescribing, naturally called Deprescribing.org. It offers a page for healthcare professionals that contains algorithms for deprescribing benzodiazepines, antipsychotics, and antihyperglycemics, all drugs with especially adverse side effects in the elderly. ■

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ABSTRACT & COMMENTARY

Insomnia Disorder: Evidence for Psychological and Behavioral Interventions

By Jessica A. Orner, MD

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

SYNOPSIS: Cognitive behavioral therapy for insomnia (CBT-I) is an effective intervention for moderate to severe insomnia disorder and should be considered as an initial treatment.

SOURCE: Brasure M, Fuchs E, MacDonald R, et al. Psychological and behavioral interventions for managing insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med* 2016;165:113-24. doi:10.7326/M15-1782.

Many Americans suffer from sleep disturbance and insomnia. Approximately 10% of people meet diagnostic criteria for insomnia disorder, and it is estimated that $30 billion is spent on insomnia treatment each year in the United States.[1,2] According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, insomnia disorder, previously known as chronic insomnia, is defined by a predominant complaint of poor sleep quantity or quality and difficulty with sleep initiation, maintaining sleep, or early morning waking with inability to return to sleep. The symptoms must cause clinically significant distress or impairment in areas of functioning. Symptoms must be present at least three nights per week for at least three months. Also, individuals must have adequate opportunity for sleep, and symptoms cannot be better explained by other conditions.[3] Options for treating insomnia disorder include pharmacologic therapies, behavioral and psychological therapies, and integrative medicine, including herbal preparations and supplements. There are several types of psychological and behavioral interventions for insomnia disorder in adults: cognitive behavioral therapy, cognitive therapy, sleep hygiene education, stimulus control, and relaxation training.[4]

Cognitive therapy aims to change how those with insomnia think about sleep and to replace dysfunctional attitudes surrounding sleep with useful beliefs.[4] Sleep hygiene education aims to educate patients about factors they can change to improve their sleep, such as limiting caffeine and maintaining a cool bedroom.[4] Relaxation training includes techniques such as progressive muscle relaxation, guided imagery, and breathing techniques.[4] CBT-I combines cognitive therapy, education, and behavioral interventions,[4] which allows for several different elements of insomnia to be addressed. In this evidence report on psychological and behavioral interventions, randomized, controlled trials published between 2004 and September 2015 were identified using bibliographic databases, including MEDLINE and the Cochrane Library. Two investigators independently reviewed the texts for the following inclusion criteria: randomized, controlled trials of psychological and behavioral interventions; adult enrollees; treatment duration of four weeks or more; published in English; and report of global or sleep outcomes. Of the 3,572 citations identified, 60 trials were analyzed. Trials were grouped by intervention type (i.e., single, multi-component) and comparison (e.g., CBT-I compared with inactive control). Insomnia Severity Index (ISI) or Pittsburgh Sleep Quality Index (PSQI) scores are two questionnaires that were used in the evaluated clinical trials to assess sleep quality and associated distress and dysfunction (i.e., global outcomes).

The American College of Physicians uses a grading system for quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development and Evaluation approach.[5] Strength of recommendation was either strong or weak. A strong recommendation indicated that the benefits clearly outweighed the risks or vice versa. A weak recommendation was given if the benefits finely balanced with the risks. Quality was graded as high, moderate, or low depending on study limitations (e.g., methodological flaws).[5] Single component interventions included one type of behavioral therapy. Examples of behavioral therapies are sleep restriction, stimulus control, and relaxation. The goal of stimulus control is to create routine sleep patterns and bedroom behaviors that promote sleep. There was insufficient evidence for most global and sleep outcomes.

However, there was low-strength evidence that showed longer total sleep time with stimulus control than with inactive controls. For multicomponent behavior therapy, which contained no cognitive component but did feature several behavioral components, there was insufficient evidence for all outcomes for the general adult population. When focusing on older adults, there appeared to be low- to moderate-strength evidence for better sleep quality based on the PSQI. Also, sleep onset was reduced by 10 minutes in this population with multicomponent behavior therapy than inactive control.

Interventions with CBT-I, which featured cognitive and behavioral components, showed improvement in most sleep outcomes across several delivery models, such as in-person, group sessions, book, handouts, or electronic resources. In the 22 trials comparing this intervention to inactive controls, 11 reported post-treatment ISI or PSQI scores. Overall, response to treatment and remission of insomnia were higher with CBT-I than inactive controls. Of the 168 people in the CBT groups, there were 89 reports of remission. Whereas, of the 159 participants in the control groups, there were 26 reports of remission ($P < 0.00001$). CBT-I sessions typically occurred once a week for one hour or less. They lasted from four to six weeks.

The authors noted several concerns and potential pitfalls. Even though these interventions are low-harm, there were no articles with high-strength evidence for psychological and behavioral interventions for insomnia disorder, and trials did not report adverse events or withdrawals from the trials routinely. The types of adverse events were not mentioned in the evidence report. Also, the authors were unable to compare different models of CBT-I delivery, such as face-to-face, internet, group therapy, or book-based. Additionally, patients in the trials presented with at least moderate to severe insomnia disorder, and trials analyzed featured well-designed CBT-I interventions with documented procedures and trained providers. Many facilities do not employ providers nor have created procedures to implement CBT-I. Both these factors lead to concern over the applicability and generalizability of the findings.

■ COMMENTARY

The latest clinical practice guideline on this subject from the American College of Physicians recommends that all adult patients receive CBT-I as the initial treatment for chronic insomnia disorder (strong recommendation, moderate-quality evidence). It also recommends shared decision-making when deciding whether to add pharmacological therapy in those for whom CBT-I was unsuccessful.[5] These recommendations are based on the evidence report reviewed above. Furthermore, the guideline states that, ideally, medications for chronic insomnia should be used no longer than four to five weeks. There is insufficient evidence to accurately weigh the benefits and harms from long-term use of medications, and it is unknown whether medications decrease the harmful effects of sleep deprivation.[5] Although medications can be useful in some populations, we know there are potential side effects, such as sleep walking, sleep eating, and engaging in intercourse while sleeping. There is also the risk of becoming physically dependent on the medications, increased risk of falls, and increased risk of mobility problems in the geriatric population. CBT-I offers a low-harm treatment option for insomnia. However, there are barriers to implementing CBT-I and other behavioral therapies on a wide scale. One barrier is identifying patients who may benefit from the intervention. Patient-completed instruments, such as the ISI, can be used in medical practices to identify candidates for CBT-I. It can help clinicians distinguish clinical from nonclinical insomnia and determine the severity, with a score of ≥ 15 meeting criteria for CBT-I intervention. Another concern with recommending CBT-I is patient access. This may be the biggest barrier to physicians recommending it. The evidence report noted that there were several models for delivery of CBT-I, but there is not enough evidence to determine which are the most effective.[4] If shown to be effective, internet-based or book-based models may provide wider access to patients. Also, few practitioners are trained in this therapy.[6] For those who are trained, insurance reimbursement is not always available. Unfortunately, there are few immediate options to overcome this barrier. Highly motivated patients may pursue out-of-pocket treatment or veterans can pursue therapy through Veteran Affairs. Regardless of the therapy used, patients likely will turn to their clinician for advice on treatment and with questions during the process. It is important that clinicians be comfortable with the evidence and current recommendations for diagnosis and treatment of chronic insomnia. ■

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PHARMACOLOGY UPDATE

Valbenazine Capsules (Ingrezza)

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

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

The FDA has approved the first drug for the treatment of tardive dyskinesia in adults. Valbenazine is a vesicular monoamine transporter inhibitor type 2 (VMAT2). Two other VMAT2 inhibitors, tetrabenazine and deutetrabenazine, are approved for chorea associated with Huntington disease. Valbenazine is marketed as Ingrezza.

INDICATIONS

Valbenazine is indicated for the treatment of tardive dyskinesia in adults.[1]

DOSAGE

The initial dose is 40 mg once daily for one week, followed by an increase to 80 mg (2 x 40 mg) once daily.[1] It may be taken without regard to meals. For these with moderate to severe hepatic dysfunction, taking a strong CYP3A4 inhibitor, or those who are poor CYP2D6 metabolizers, the dose should be 40 mg. Valbenazine is available as 40 mg capsules.

POTENTIAL ADVANTAGES

Valbenazine is the only approved drug for tardive dyskinesia.

POTENTIAL DISADVANTAGES

The most common adverse reaction (vs. placebo) is somnolence (11% vs. 4%).[1] Clinically significant QT interval prolongation may occur in patients taking strong CYP2D6 or CYP3A4 inhibitors or who are poor CYP2D6 metabolizers.

Valbenazine should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with prolonged QT interval. Concomitant use with a strong CYPA4 inducer is not recommended.

COMMENTS

Tardive dyskinesia is believed to result from upregulation of postsynaptic dopamine receptors due to long-standing blockade by dopamine-blocking drugs.[2,3] VMAT2 is a protein/transporter in the neurons that regulates the storage, packaging, and release of dopamine into the synapse. Inhibitors of VMAT2 decrease the amount of dopamine released. Valbenazine does not appear to exhibit appreciable affinity to dopaminergic, serotonergic, muscarinic, or histaminergic receptors.[1]

The efficacy of valbenazine was evaluated in a double-blind, placebo-controlled trial in 234 subjects with moderate to severe tardive dyskinesia.[1,4] These subjects presented with schizophrenia, schizoaffective disorder, or mood disorder of three months or greater duration and dopamine receptor blocker-induced tardive dyskinesia. Subjects were randomized to valbenazine 40 mg, 80 mg, or placebo. The primary endpoint was change from baseline to week six on the sum of items 1-7 of the Abnormal Involuntary Movement Scale (AIMS dyskinesia score). Items 1-7 assess the severity of involuntary movements across body regions (scored 0-4).

Overall mean baseline AIMS dyskinesia score was about 10.0 ± 4.0. Mean changes at endpoint compared to placebo were -1.8 for 40 mg (effect size, 0.53) and -3.1 for 80 mg (effect size, 0.90). AIMS dyskinesia responses (≥ 50% reduction) were 23.8%, 40.0%, and 8.7%, respectively, for the 40 mg dose, 80 mg dose, and placebo. This translates to a number needed to treat of 4 for the 80 mg dose. Effect for the 80 mg was observed in week two. The psychiatric status of subjects remained stable at the two-week washout period after the six-week treatment.[3] The drug appears to be well-tolerated, as only two subjects assigned to the 80 mg aim required a dose reduction and 3% of taking valbenazine discontinued treatment compare to 2% for placebo. Treatment effect appeared to be maintained for 42 weeks in an extension study. AIMS dyskinesia scores revert toward baseline after discontinuation of treatment.[1] A 72-week rollover study is in progress.[5]

CLINICAL IMPLICATIONS

Tardive dyskinesia is a potentially disabling neurological disorder characterized by repetitive involuntary movements, including grimacing, sticking out the tongue, and lip smacking.[6] Often, it is associated with use of antipsychotics, with an annual incidence of 8.5% for typical antipsychotics and 3.1% for atypical antipsychotics.[2] Currently, treatment options for tardive syndromes are limited; the American Academy of Neurology lists amantadine and tetrabenazine as possibly effective for short-term use.[7] Valbenazine is the first drug approved for tardive dyskinesia. It appears to be effective, with a favorable benefit-to-risk ratio. The cost was not available at the time of this review. ■

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CME QUESTIONS

1. An obese patient who routinely develops heartburn after eating a large Mexican dinner two hours before bedtime should *not* be advised to:
a. begin taking omeprazole daily.
b. lose weight.
c. avoid dietary triggers.
d. avoid eating before bedtime.
e. sleep in the reverse Trendelenburg position.

2. Which of the following is recommended by the American College of Physicians when considering interventions for insomnia disorder?
a. Cognitive behavior therapy for insomnia (CBT-I) should be considered after other interventions, like benzodiazepines or hypnotics, have failed.
b. Pharmacological therapy should be initiated at the same time as CBT-I to have the most beneficial effect.
c. Clinicians should use shared decision-making when considering whether to add pharmacological therapy if CBT-I is unsuccessful.
d. Cognitive behavioral therapy is recommended as the initial treatment for mild insomnia disorder.

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.

Clinical Briefs

By Louis Kuritzky, MD

Testosterone Replacement: The Limitations of 'Dr. Google'

SOURCE: McBride JA, Carson CC, Coward RM. *Int J Impot Res* 2017;29:110-114.

The availability of information at the touch of a finger has become a mixed blessing. Clinicians applaud patients' efforts to become more involved and informed about their health, but are chagrined about the frequency with which transmission of misinformation occurs.

McBride et al performed a review of websites offering information on hypogonadism by searching the terms "testosterone," "testosterone therapy," and "hypogonadism." Then, the authors performed a quality review on the information supplied by the top 25 websites listed. To keep the subject matter within the most commonly addressed bounds that would be expected to provide relevant information, advertising sites, clinical practice guidelines, and pharmaceutical company websites were omitted. Information was rated for readability (e.g., was the reading level appropriate for most adults), credibility (e.g., who authored the information, references, physician-confirmed medical accuracy, and currency), and quality (e.g., were there links to other educational resources, and were risks as well as benefits appropriately disclosed).

Based on their "internet biopsy," the authors reached an unfortunate conclusion: Information online was of poor quality and of a complexity level beyond the comprehension of the average patient. Clinicians may have to take a role in directing patients toward high-quality online information. ■

The Ever-evolving Status of Prostate Cancer Screening

SOURCE: Bibbins-Domingo K, Grossman DC, Curry SJ. *JAMA* 2017;317:1949-1950.

The most recent 2017 U.S. Preventive Services Task Force (USPSTF) recommendations regarding prostate cancer screening, which still are open to comment and revision, represent a shift from its "do not screen" statement of 2012. At first glance, the advice may appear to be an "endorsement"; however, one must remember that there are various strengths of endorsement. For instance, the current recommendation boils down to: "Clinicians should inform men aged 55-69 about the potential benefits and harms of screening." Benefits include about one in 1,000 fewer deaths from prostate cancer and three in 1,000 fewer incidences of metastatic disease when men are followed for 12-13 years. Well-publicized harms include impotence and urinary incontinence.

One's enthusiasm for the newer, more sanguine recommendations rightly might be damped by noting that this recommendation is graded as "Level C." What does that mean? In the words of the USPSTF: "The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small."

In other words, each patient must decide whether he is willing to shoulder the risks associated with prostate cancer screening for the possibility that he will be one of the very few men who benefit, which is not an easy call. ■

Send Polycystic Ovary Syndrome Patients to the Dentist?

SOURCE: Kellesarian SV, Malignaggi VR, Kellesarian TV, et al. *Int J Impotence Res* 2017;29:89-95.

We are becoming progressively enlightened about the intimate relationship between the microbiome (healthy "constitutive" bacteria throughout the body, particularly the gastrointestinal tract) and health. Periodontal disease is a local inflammatory disorder with wide-ranging consequences. It is associated with increased expression of systemic vascular adhesion molecules, tumor necrosis factor, and interleukins. Downstream effects of periodontal disease lead to endothelial dysfunction and have been linked to atherosclerosis, myocardial infarction, stroke, type 2 diabetes, and hypogonadism. This literature review by Kellesarian et al suggested an additional consequence of periodontal disease: polycystic ovary syndrome (PCOS).

Seven case-controlled studies of subjects (n = 770) with PCOS who had undergone evaluation for periodontal health provided the data for evaluation. In each of the studies, a positive association was found between PCOS and periodontal disease.

The link between PCOS and diabetes is well established. These data are limited by the fact that the only available clinical data come from relatively small, short-term trials. Nonetheless, the authors suggested that the consistency of the results (all seven trials found the same positive association) should prompt clinicians to refer PCOS patients for assessment of periodontal health. ■

Internal Medicine [ALERT]

ECG Review

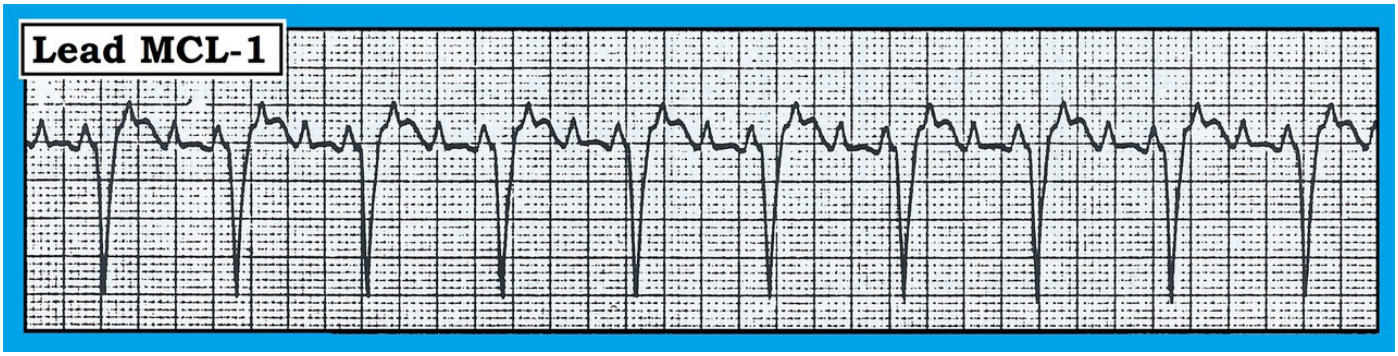
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

Is This a Typical Flutter?

The rhythm in the figure below was diagnosed as atrial flutter. Do you agree? If so, is there anything unusual about this rhythm strip?



Atrial flutter is characterized by a special pattern of regular atrial activity that in adults almost always occurs at a rate of 300/minute (250-350/minute range). The most common ventricular response to atrial flutter by far is with 2:1 AV conduction. As a result, the ventricular rate with untreated atrial flutter usually will be close to 150/minute (i.e., 300 ÷ 2), although the ventricular rate may be slower if the patient is taking antiarrhythmic drugs.

Less commonly with atrial flutter, there is 4:1 AV conduction (ventricular rate ~75/minute) or a variable ventricular response. Odd conduction ratios (i.e., 1:1: or 3:1 or 5:1) are possible but extremely uncommon unless the patient is on antiarrhythmic medication or has Wolff-Parkinson-White syndrome.

Atrial flutter typically manifests a sawtooth appearance that usually is best seen in the inferior leads. That said, flutter waves sometimes may be subtle and only seen in a handful of leads (if at all). Distinction between atrial tachycardia and atrial flutter may be difficult.

This is especially true when the characteristic sawtooth appearance of flutter is missing, and the rate of atrial activity is at least slightly below the usual range for flutter.

The ventricular response in the figure is regular at a rate of ~85/minute. Regular atrial activity is seen, but instead of two P waves for each QRS, there are three P waves for each QRS complex. Note that the PR interval preceding each QRS complex is the same. This tells us that there is conduction, in this case with a 3:1 ratio (i.e., one out of every three P waves seen within each R-R interval is conducted to the ventricles).

Since we know that there are three times as many P waves as QRS complexes in this example, the easiest way to accurately calculate the atrial rate is to multiply the ventricular rate (85/minute) by 3. This yields an atrial rate ~255/minute, which is above the usual range for atrial tachycardia. As a result, the rhythm in the figure most likely represents the unusual case of atrial flutter with the odd conduction ratio of 3:1.

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