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# Internal Medicine

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ABSTRACT & COMMENTARY

## Safe Treatment Recommendations for Benzodiazepine Dependence

***By Tim Drake, PharmD, MBA, BCPS, and Martin S. Lipsky, MD***

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**Drs. Drake and Lipsky report no financial relationships relevant to this field of study.**

SYNOPSIS: There are clear, evidence-based treatment withdrawal regimens for benzodiazepine-dependent patients.

SOURCE: Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med* 2017;376:1147-1157.

Benzodiazepines bind to the gamma-aminobutyric acid type A receptor, increasing the receptor's affinity for gamma-aminobutyric acid, which causes an inhibitory effect in the central nervous system. They have been used since the 1960s for their anxiolytic, hypnotic, anticonvulsant, amnesic, and muscle-relaxant effects. Benzodiazepines by themselves are fairly safe, especially when used for less than two to four weeks. Dependence can develop in patients who use them for longer than one month. Common side effects include drowsiness, lethargy, fatigue, stupor, and disturbances in concentration and attention. Contraindications include myasthenia gravis, ataxia, sleep apnea, chronic respiratory insufficiency, and angle closure glaucoma. Because of the increase in falls, fractures, and cognitive decline, benzodiazepines should be avoided in the elderly. Physical and mental dependence can occur with benzodiazepine use, even if tolerance does not develop. Common signs of dependence include doctor or pharmacy shopping and/or early refills or overlapping prescriptions. Characteristics of long-term benzodiazepine use include: age > 65 years, prescribed by a psychiatrist, regular use, use of a high dose, and use of other psychotropic medications. Physical withdrawal symptoms include muscle tension, weakness, spasms, pain, flu-like symptoms, and a "pins and needles" sensation. Psychological withdrawal symptoms include anxiety or panic disorders, agitation, depression, mood swings, tremor, reduced concentration, and sleep disturbances.

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The most serious withdrawal complication is seizures, which can develop with abrupt withdrawal.[1]

To avoid withdrawal, benzodiazepines should be tapered over four to six weeks or more for higher doses (> 30 mg per day of diazepam). The taper rate should be based on the patient's ability to tolerate symptoms and can be done by decreasing the dose by 50% each week or by a 10-25% overall reduction every one to two weeks. A withdrawal schedule with precise dosing recommendations, along with medications to treat symptoms or coexisting conditions, can be helpful. For depression or chronic anxiety, a serotonin reuptake inhibitor is recommended. Trazodone or doxepin can be used to treat insomnia. Pregabalin, gabapentin, and beta-blockers can be tried as alternative anxiolytic agents, but caution is advised with pregabalin because of abuse potential. Switching from a short-acting benzodiazepine to a long-acting agent makes sense, but has not been proven useful clinically. Additionally, the use of the benzodiazepine antagonist flumazenil has not shown benefit and may induce seizures.[1]

Psychotherapy should be included in the plan to support the withdrawal process, to facilitate further abstinence, and to treat the underlying disorder. Cognitive behavioral therapy has the most evidence supporting its use and is the most widely used treatment for benzodiazepine withdrawal. Components of this therapy should include social competence training, relaxation techniques, training to overcome anxiety, and other behavioral therapy approaches. Other approaches include motivational interviewing, although the evidence is insufficient to support its use on an outpatient basis. Motivational techniques are more useful for inpatient treatment, whereas group or individual psychotherapeutic techniques are more useful on an outpatient basis.[1]

## ■ COMMENTARY

Benzodiazepine use has substantially increased in the past 10 years. Consequently, it is not surprising that deaths from overdose also increased from 0.58 in 1996 to 3.07 deaths per 100,000 adults in 2013.[2] Additionally, 46-71% of patients receiving opioid maintenance therapy use benzodiazepines,[3] which is concerning since the combination increases the risk of respiratory depression.

The FDA recently released a statement that the prescribing information for opioid analgesics and benzodiazepines will be changed to include the following statement: "Concomitant use of opioid pain or cough medicines and benzodiazepines, other central nervous system depressants, or alcohol may result in profound sedation, respiratory depression, coma, and/or death."[4] Also, the combination of opioids and benzodiazepines should be reserved for patients who have failed alternative treatments. This change will result in the need for many patients to either taper off their opioids or benzodiazepines. Tapering one agent, either the opioid or the benzodiazepine, should be accomplished before beginning to taper the other agent. Because of the possible dependence, benzodiazepines should be used with caution to treat the side effects of opioid withdrawal.

"There is a striking discrepancy between the high prevalence of benzodiazepine dependence and the very low treatment rates, especially in addiction service centers."[5] Although there have been many advertisements, health statements, and political statements about the opioid epidemic, there is little marketing on the use or abuse of benzodiazepines. Many opioid-related deaths involve the concomitant use of alcohol or benzodiazepines. Maybe a portion of the funds used to educate the public about the appropriate use of opioids also should be used to educate about the potential problems associated with the long-term use of benzodiazepines. ■

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ABSTRACT & COMMENTARY

# Risk Factors for Hospital Readmissions Ending in Death or Transition to Hospice

*By Betty Tran, MD, MSc*

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

SYNOPSIS: In this retrospective cohort study, multiple factors were identified during initial hospitalization, including sepsis and shock, that were associated with a hospital readmission within 30 days resulting in death or transition to hospice. Infection was a frequent cause for readmissions that ended in death.

SOURCE: Dietz BW, Jones TK, Small DS, et al. The relationship between index hospitalizations, sepsis, and death or transition to hospice care during 30-day hospital readmissions. *Med Care* 2017;55:362-370.

Recently, nationwide efforts have focused on reducing hospital readmissions in hopes of reducing costs, morbidity, and mortality, as well as improving quality of care. Identifying risk factors present during an index hospitalization that are associated with 30-day readmissions that result in death or transition to hospice may inform the development of strategies that potentially could reduce readmission rates and/or facilitate transitions to hospice care outside the acute care setting.

In this retrospective cohort study from authors at the University of Pennsylvania Health System, 17,716 readmissions within 30 days were evaluated. Of these, 1,144 readmissions (6.5%) expired or transitioned to hospice care.

After adjustment for potential confounders, factors during the index hospitalization that were associated with in-hospital death or transition to hospice care during 30-day readmission included: age, insurance status, comorbidities as measured by the Charlson Comorbidity Index (especially a diagnosis of malignancy), number of hospitalizations in the prior year, non-elective admission type, outside hospital transfer, low discharge hemoglobin and sodium, high discharge red blood cell distribution width, and disposition to home with home health services or to skilled care facilities.

In addition, sepsis and shock during the index hospitalization were associated with increased in-hospital mortality or transition to hospice during 30-day hospital readmission with an odds ratio of 1.33 (95% confidence interval [CI], 1.02-1.72; $P = 0.03$) and 1.78 (95% CI, 1.22-2.58; $P = 0.002$), respectively.

Among 30-day readmissions resulting in death, compared to index non-sepsis hospitalizations, infection was more likely to be the primary cause for readmission among those with an index sepsis hospitalization (51.6% vs. 28.6%; $P = 0.009$).

Among the 125 cases that resulted in death during a 30-day hospital readmission, 90.4% were admitted to the ICU and 78.4% received mechanical ventilation. Among 30-day hospital readmissions after an index hospitalization for sepsis, factors that were present during the index hospitalization associated with death or transition to hospice during readmission included age, malignancy, more than five hospitalizations in the prior year, and discharge to a long-term acute care facility.

## ■ COMMENTARY

This study highlights factors that are associated with an increased risk of hospital readmission within 30 days and adds to the growing body of literature on healthcare use after a hospitalization for sepsis summarized in this month's Special Feature.

Many of the risk factors found, such as age, comorbidities, and high number of hospitalizations, are not surprising, while others, such as discharge hemoglobin and sodium, may track with age and/or comorbidities.

The finding that sepsis and shock were associated with increased risk of 30-day hospital readmission resulting in death or transition to hospice, with infection identified as a frequent primary cause for readmission, also is consistent with findings previously reported.

However, the challenge lies in using these findings in meaningful ways. To what extent hospital readmissions can be prevented is unclear, as these risk factors may identify patients who are on an inevitable downhill trajectory of health leading up to single or multiple hospital readmissions. Theoretically, this at-risk population could be targeted for improved post-discharge coordination of care, including timely and accurate discharge summaries, enhanced communication between acute care and post-discharge health providers, and early and intensive nursing and physician follow-up.

In addition, for many of these patients, palliative care consultation during the index hospitalization could provide not only additional support but also a strategy that could explore patient goals and values and potentially lead to earlier hospice referrals and discharge to home or inpatient hospice units rather than hospital readmission.

Future studies exploring whether these interventions produce an effect on hospital readmission rates will be critical. ■

ABSTRACT & COMMENTARY

# Fludrocortisone for Orthostatic Hypotension Associated with Parkinson's Disease

*By Harini Sarva, MD*

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

SYNOPSIS: This double-center, double-blind, randomized, controlled trial compared the efficacy of pyridostigmine bromide vs. fludrocortisone and demonstrated that pyridostigmine bromide was not as effective as fludrocortisone. The authors also provided evidence for the efficacy of fludrocortisone in treating neurogenic orthostatic hypotension.

SOURCE: Schreglmann SR, Buchele F, Sommerauer M, et al. Pyridostigmine bromide versus fludrocortisone in the treatment of orthostatic hypotension in Parkinson's disease. *Eur J Neurol* 2017;24:545-551.

This double-center, double-blind, randomized, controlled trial compared the efficacy of pyridostigmine bromide (PB) with fludrocortisone for orthostatic hypotension (OH) in Parkinson's disease (PD). It was a Phase II, non-inferiority trial that included patients aged 50-80 years with a diagnosis of PD according to the U.K. Brain Bank Criteria and symptomatic OH (systolic blood pressure [SBP] drop by ≥ 20 mmHg or diastolic blood pressure [DBP] drop by ≥ 10 mmHg within three minutes of standing). Patients on medications that regulate blood pressure, with systemic diseases such as diabetes mellitus, or with clinical features of cerebellar involvement or multiple system atrophy (MSA) were excluded. The two trial arms were of 14 days duration and the subsequent washout was 21 days prior to crossover. Visits were conducted immediately before drug initiation and immediately after the final dose. The following were performed on the subjects: UPDRS Part III for motor assessment, Montreal Cognitive Assessment, Hospital Anxiety and Depression Scale, Zurich autonomic questionnaire, Orthostatic Hypotension Severity Assessment, non-invasive central blood pressure measures using pulse wave analysis by applanation tonometry, and cardiovascular monitoring using the Schellong maneuver. Home blood pressure in the sitting position consisted of automated repeat morning and evening measurements for seven days. PB was started at 90 mg per day for three days before increasing to 180 mg per day. Fludrocortisone was started at 0.1 mg per day before increasing to 0.2 mg per day after three days. Drug calendars and collection of empty medication boxes were used to assess drug compliance. Thirteen patients were recruited and four dropped out. After an interim analysis showed futility of PB in comparison to fludrocortisone, researchers ended the study and performed an intent-to-treat analysis. Fludrocortisone improved the primary outcome measure of improvement in DBP drop by 37% as assessed by Schellong maneuver and mean arterial blood pressure standing by 15%, whereas PB had no significant effect. Peripheral SBP supine and SBP home measurements improved by 11% with fludrocortisone, but there was no effect with PB. However, subjective symptom severity did not correlate with the numerical improvements. Although PB lowered central mean supine blood pressure, it remained unchanged with fludrocortisone. Neither demonstrated any significant improvement on motor, cognitive, or psychiatric assessments. Transient adverse events were mild for each drug and did not cause study dropout.

## ■ COMMENTARY

Orthostatic hypotension remains a major quality-of-life issue for patients with PD. Although clinicians try conservative measures prior to starting medications such as fludrocortisone, midodrine, and now droxidopa, consensus on which medication to choose and dosing still remains an issue. Much of the evidence for using these medications comes from relatively small studies with subjects exhibiting various causes of neurogenic orthostatic hypotension, such as MSA and pure autonomic failure. Difficulty in recruitment, along with various means of measuring blood pressure changes, remain major challenges to defining precise algorithms. In addition, the pathological mechanisms of developing OH in the various conditions is different. In MSA, the lesion site is central and preganglionic, whereas in PD it is peripheral and postganglionic, further adding to the complexity of

OH and developing consensus management strategies. In addition, difficulty in accurately measuring central blood pressure changes and their role in accurately predicting vascular response to treatments of orthostatic hypotension have not been well-studied in PD. This study is important in that it shows that fludrocortisone is effective in treating OH in PD, albeit in a small sample size, and that it may not increase central blood pressure, suggesting that it is a relatively safe treatment. However, the small sample size and the relatively large dropout rate are major limitations of this study. Further evidence is required to first set up a consensus for accurate BP measurements in PD patients and then to provide an appropriate treatment algorithm. For now, it is still important to exhaust conservative measures, such as increasing salt and fluid intake, using compression stockings, reducing antihypertensives, and possibly adjusting the dose of dopaminergic medications, before initiating blood pressure-raising medications. Anecdotally, we know that improving OH can improve motor and cognitive symptoms, and further research in this area also is needed to determine when blood pressure support should be initiated to improve quality of life and functionality. ■

PHARMACOLOGY UPDATE

# Brigatinib Tablets (Alunbrig)

***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 third drug in the class of second-generation, orally active, anaplastic lymphoma kinase (ALK) inhibitors for the treatment of ALK-positive non-small cell lung cancer (NSCLC), joining alectinib and ceritinib. The FDA granted brigatinib breakthrough therapy, orphan drug designation, priority review, and accelerated approval. An accelerated approval is based on tumor response rate and duration of response. Continued approval may be contingent on verification and description of clinical benefit in a confirmatory trial.[1] It is marketed as Alunbrig.

## INDICATIONS

Brigatinib is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.[1]

## DOSAGE

The recommended dose is 90 mg daily for the first seven days, and if tolerated, increase to 180 mg once daily.[1] It may be taken without regard to meals. Patients take brigatinib until there is disease progression or unacceptable toxicity.

Dose modification due to the nature and severity of adverse events is detailed in the prescribing information.[1] Brigatinib is available as 30 mg and 90 mg tablets.

## POTENTIAL ADVANTAGES

Brigatinib is more potent than crizotinib and provides another option in targeting crizotinib-resistant mutations.[2,3] It appears to target the most common resistant mutation, G1202R, found in patients progressing on second-generation ALK-tyrosine kinase inhibitors (TKI).[2-4]

## POTENTIAL DISADVANTAGES

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease have occurred with a frequency of 4-9%, depending on the dosage regimen.[1] Other adverse events can include hypertension (11-21%), bradycardia (6-8%), visual disturbance (7-10%), creatine phosphokinase elevation (27-48%), pancreatic enzyme elevation (27-39%), and new or worsening hyperglycemia (43%). Adverse events resulted in a discontinuation rate of 8.2% with the recommended dose. Coadministration with strong CYP3A inhibitors or inducers should be avoided.

## COMMENTS

The accelerated approval for brigatinib was based on a randomized, Phase II trial in subjects with locally advanced or metastatic ALK-positive NSCLC that progressed on crizotinib and documented ALK rearrangement.[1,5] Ninety-eight percent had stage IV disease, 69% had brain metastases, and 64% had objective response to crizotinib. Subjects were randomized to two arms: brigatinib 90 mg once daily (n = 112) or 180 mg once daily with a seven-day lead-in period (n =110) and stratified by the presence of brain metastases. Primary efficacy endpoint was confirmed overall response rate (ORR) as evaluated by an Independent Review Committee based on Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional outcomes included duration of response (DOR) and intracranial ORR and DOR. Endpoints also were measured based on investigator assessment. After a median follow-up of eight months, ORRs were 48% for the lower dose and 53% for the higher dose. Responses were mainly partial, 45% vs. 48%, and DOR was 13.8 months for both arms. Results from investigator assessments were similar. For

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those stratified with measurable brain metastases, intracranial ORRs were 42% vs. 67% and partial response rates, 35% vs. 67%, respectively.

## CLINICAL IMPLICATIONS

Lung cancer is the second most common cancer worldwide, with 85-90% classified as NSCLC. Approximately 3-7% of NSCLC showed ALK rearrangement.[6] Currently, the National Comprehensive Cancer Network recommends crizotinib or ceritinib as first-line therapy.[7] For those who progress, ceritinib or alectinib are recommended as subsequent therapy. Resistance to AKL-TKIs may result from ALK gene mutation or activation of alternative signaling pathways bypassing ALK. Brigatinib is the newest addition to the second-generation ALK-TKIs. These agents generally are more potent than crizotinib and active against brain metastasis.[4] There may be differences in adverse reaction profiles as the frequency of gastrointestinal adverse events and elevation of AST/ALT are lower for alectinib and brigatinib compared to ceritinib.[4] Brigatinib may have the benefit of the ability to overcome a common resistant mutation of the second-generation agents. Its ultimate role in therapy remains to be determined. A Phase III comparison trial to crizotinib is in progress in ALK-positive (ALK inhibitor-naïve) NSCLC subjects, with results expected in 2021.[8] The cost for brigatinib is $17,100 for a 30-day supply of 180 mg per day. ■

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## CME QUESTIONS

1. **Which statement about benzodiazepines is true?**
   a. Deaths from benzodiazepine overdose have increased from 0.58 in 1996 to 3.07 deaths per 100,000 adults in 2013.
   b. Benzodiazepines should be tapered over a two- to four-week period.
   c. The most serious complication of benzodiazepine withdrawal is seizures.
   d. Switching from a short-acting to a long-acting benzodiazepine reduces the risk of withdrawal symptoms.
   e. Both a and c are true.
2. **In the study by Dietz et al, all the following factors present during an index hospitalization were associated with death or transition to hospice during 30-day readmission *except*:**
   a. age.
   b. marital status.
   c. sepsis.
   d. insurance status.
   e. number of prior hospitalizations.
3. **Among patients who died during a 30-day readmission, what was the primary cause for readmission in patients initially hospitalized for sepsis?**
   a. Infection
   b. Myocardial infarction
   c. Acute respiratory failure
   d. Acute renal failure
   e. Weakness
4. **Which of the following is true regarding fludrocortisone in comparison with pyridostigmine bromide?**
   a. It reduced mean arterial blood pressure standing.
   b. It improved mean diastolic blood pressure drop by 15%.
   c. It improved diastolic blood pressure drop by 37%.
   d. It increased central blood pressure measurements.

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# Clinical Briefs

By Louis Kuritzky, MD

## Liraglutide for Prevention of Diabetes

SOURCE: le Roux CW, et al. *Lancet* 2017;389:1399-1409.

Prevention of progression from prediabetes (pDM) to type 2 diabetes mellitus (T2DM) is quite a success story. Essentially, each antidiabetic entity that has been trialed (and some weight loss agents) has provided a substantial reduction in the risk of progression from pDM to T2DM. Untreated, clinicians could expect that (in the United States) 6-10% of untreated pDM patients per year will progress to T2DM if no intervention occurs; that number can be reduced by about 25% through several T2DM medications, including metformin, and even more by an intensive program of diet and exercise.

The newest agent to be added to the list of successful agents is liraglutide. In a study of pDM patients (n = 2,254) randomized to liraglutide or placebo and followed for up to three years, incidence of T2DM was 6% in the placebo group vs. 2% in the liraglutide group.

The study subjects in this trial were enrolled multinationally, including countries in Europe, North and South America, Asia, Africa, and Australia. The dose of liraglutide used would be regarded as the "weight-loss dose"; that is, liraglutide under the trade name of Victoza is prescribed for treatment of T2DM up to 1.8 mg/day, but under the trade name of Saxenda is prescribed at 3 mg/day for the treatment of obesity. As would be anticipated, liraglutide treatment produced a significant weight loss: approximately 5 kg greater than the placebo group.

Currently, the most popular pharmacologic treatment for prevention of T2DM in patients with prediabetes is metformin. Several other agents have been shown to produce similar effects, although their use would be off-label. ■

## Surgical Replacement: Younger vs. Older Knees and Hips

SOURCE: Bayliss LE, et al. *Lancet* 2017;389:1424-1430.

Most patients I have seen who have undergone hip or knee replacement experienced prompt restoration of function and marked reductions in pain. In advanced osteoarthritis sufferers who are as yet untreated surgically, the question often becomes "Should I do it sooner or later?" Waiting until later often entails enduring a significant symptom burden as well as limited mobility; doing it sooner may feel premature to patients with moderately disabling symptoms.

Bayliss et al provided substantiation for "doing it later" (i.e., later by one's chronologic clock). They assessed data on more than 63,000 individuals who had undergone hip or knee replacement. Hip and knee replacements were shown to be very durable, in that more than 95% of hip or knee replacements were functioning 10 years later, and more than 85% were functioning 20 years later.

However, when specifically looking at the relationship between age at intervention and need for revision, they found that study subjects > 70 years of age who underwent joint replacement surgery experienced a seven-fold lower incidence of revision than patients ≤ 50 years of age (5% lifetime revision rate for the former vs. 35% for the latter). Although the joint replacement decision always should be individualized, these data suggest that we inform potential subjects of the greater likelihood for repeat surgery if initial surgery is performed on patients < 70 years of age. ■

## Spinal Manipulation for Low Back Pain

SOURCE: Paige NM, et al. *JAMA* 2017;317:1451-1460.

Several interventions for low back pain (LBP) have been demonstrated to improve time to resolution modestly, but no particular treatment has been identified that provides a strong therapeutic advantage over another consistently. Analgesics, anti-inflammatory agents, muscle relaxants, exercise, physical therapy, and spinal manipulation therapy (SMT) each have supportive evidence for efficacy, but SMT has been the object of contentious arguments.

Paige et al reviewed the efficacy and safety of SMT by including 15 randomized, controlled trials (n = 1,711). They concluded that SMT provides a modest statistically significant improvement in pain: approximately 10 points on a 100-point visual analogue scale. They described the harms of SMT as generally transient and minor. Whether the degree of pain reduction attributed to SMT reported here will satisfy many clinicians is questionable. Previous evidence has indicated that at least a 30% reduction in pain from baseline is what patients recognize as clinically meaningful, and these data only indicate a 10% pain reduction. Additionally, the serious adverse effects that have been noted about high-velocity manual medicine techniques (e.g., arterial dissections and paralysis after cervical spine manipulation) occur with insufficient frequency to be reliably detected within such a limited data set. ■

Internal Medicine [ALERT]

# ECG Review

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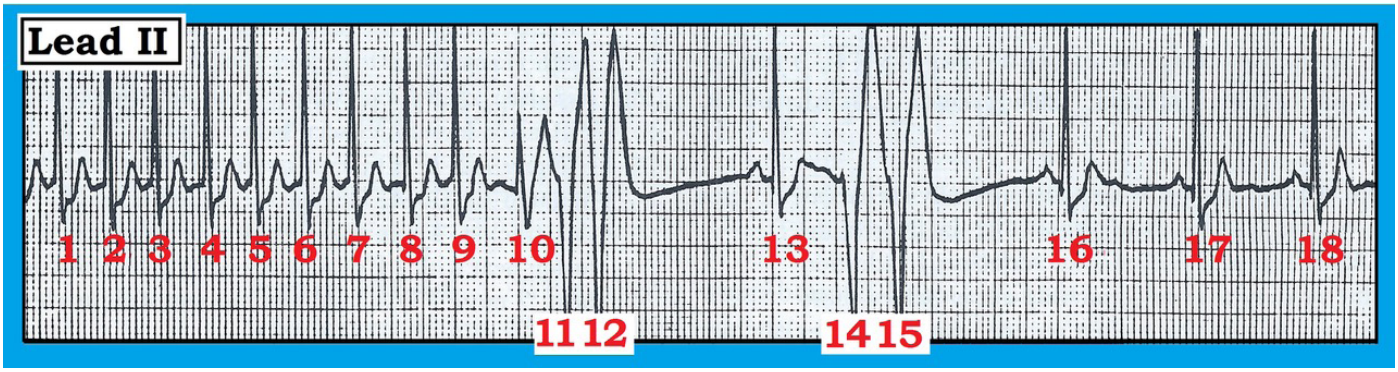
## Should the Treatment Response Cause Alarm?

The rhythm in the figure below was observed as a previously healthy young adult was receiving treatment for his "palpitations." He was hemodynamically stable at the time.




Should what we see be cause for alarm? The patient is hemodynamically stable. The first nine beats show a regular supraventricular tachycardia (SVT) rhythm at a rate of 185-190 beats/minute. No atrial activity is seen during this run. The rhythm changes beginning with beat #10.

After the run of SVT, it is easiest to look next at beats #11 and #12. Both beats clearly are ventricular, since the QRS complex is wider and completely different in appearance from QRS complexes during the SVT run at the beginning of the tracing.

Beat #10 manifests an intermediate morphology, both of the QRS complex and of the ST-T wave, between the narrow beats before it and the ventricular couplet that follows. Beat #10 is a fusion beat, which means it is due to simultaneous occurrence of a supraventricular and ventricular beat. Therefore, beats #10-12 constitute a three-beat salvo of ventricular tachycardia.

Sinus rhythm then is seen to occur beginning with beat #13. Another ventricular couplet follows (beats #14 and #15), with the tracing ending in a regular sinus rhythm at a normal rate.

The rhythm in the figure begins with a nine-beat run of atrioventricular nodal reentry tachycardia (AVNRT). The rate of this SVT rhythm is too fast for atrial flutter, with a 2:1 conduction. Sinus tachycardia rarely goes this fast. Abrupt conversion to sinus rhythm (beat #13) supports the diagnosis of AVNRT, which is a common cause of "palpitations" in the young adult age group.

We do not know if conversion to sinus rhythm was achieved by a vagal maneuver, by medication, or by a combination of the two. Regardless, the point to emphasize is that it is a common and normal phenomenon to see PVCs (including ventricular couplets or salvos) at the time of conversion from a reentry tachycardia to sinus rhythm. This is not cause for concern and should not prompt additional workup.

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