RESTLESS LEG SYNDROME
AND
PERIODIC LEG MOVEMENTS

Sleep Overview

It has been roughly estimated that 20 to 25 percent of our society, or 70 million Americans, have some sort of sleep complaint. The effects of loss or dysfunctional sleep can have devastating consequences on memory consolidation, learning, mood, attention, behavior, safety, and quality of life. In some sleep disorders, such as sleep apnea, huge pathological and outcome data on many organ systems have come into play. Many of the important sleep disorders were left out of any medical school curriculum as they really have just in the last couple of decades come into the focus in a well-dispersed specialty. And for that reason they can be a “hole” in our otherwise well-rounded knowledge of medicine.

Our goal for today is to play the “90 Percent Rule.” The top three to four diseases usually make up 90 percent of the diagnosis in this category. If we can recognize, diagnose, and treat those, we have made a huge dent in any disease category. If it does not “shake out” in that first pass, then it is probably not worth your trouble, and is one of those things that it is easier to refer to a specialist in that area to sort through.

Definitely, the most important sleep disorder to become familiar with is sleep apnea and Dr. Rattin will dedicate a whole lecture to it and its secondary disastrous consequences.

I will review the most common movement disorders, i.e., restless leg syndrome and periodic leg movements. Additionally, I will cover the most important parasomnias (“around sleep,” or better stated, things that go bump in the night), specifically rapid eye movement (REM) behavior disorder and then very briefly
sleep walking, confusional arousals, and nocturnal seizures. Each one of these topics could be a multi-hour review by itself with a very long manuscript to discuss its intrigoses, but that is not our goal for the day. Additionally, there are other rare movement disorders and parasomnias that I will not even mention. What I hope to share is the “bare bones” diagnostic strategies, the pitfalls, and solutions to diagnose and treat these sleep disorders that you will definitely see in your practice and count on you to recognize that if something falls out of the “90 Percent Rule,” you will need to refer out. If it does not “feel right” after this approach, then seeking out consultation would be the right answer. There are many great reviews, and I have tried to list some of the key articles and chapters in the bibliography.

Restless Leg Syndrome and Periodic Leg Movements

It is my opinion that restless leg syndrome (RLS) is both under diagnosed and over diagnosed. It is a real syndrome that can have terrible adverse consequences on both the individual and the bed partner leading to hypersomulence (sleepiness) and insomnia (both “sleep onset” at the beginning of the sleep period and “sleep maintenance,” waking you up in the middle of the night). With mass TV advertising by the pharmaceutical industry, now everybody and their brother thinks that they have RLS, and that anything that moves in the bed must be RLS. The drugs for this syndrome have been a great breakthrough, but in turn have had great side effects, some disastrous.

The true incidence of RLS is unknown. Studies have ranged from 2.7 percent to 25 percent of society. Many authorities roughly quote a ten percent incidence of RLS. Most of these studies are questionnaires as RLS is a clinical diagnosis without a confirmational test. So, who wrote the questionnaire, who led the
interview, who took the time to fill it out, and who decided what was significant is the basis of this type of research. One of the largest studies of the USA and six European countries used a validated 30-question survey of over 15,000 people and showed patients with any symptoms having a rate of approximately 7 percent. When at least two episodes per week of “moderate” severity occurred, the rate came down to 2.7 percent. Of these moderate to severe cases, 80 percent had complained to their physicians and only six percent had been diagnosed. Hence the “under diagnosed” nature of this disease.

Defining RLS is difficult, and many important reviews and textbooks use terms like “sensation that is difficult to describe.” In a “nutshell” or using the “90 Percent Rule,” RLS is a sensory motor syndrome of the legs, or a parasthesia that is associated with an uncontrollable urge to move one’s legs. The sensation worsens as one approaches the sleep period of the day and usually comes on as one settles down for the night, but can be brought on by resting or sitting at movies, and ball games, etc. The sensation is made better by moving. It is best defined as a “pre-sleep” syndrome. This diagnosis is made BEFORE one goes to sleep. It can extend into sleep with periodic leg movements (PLMS) that can lead to arousals or awakenings, can cause terrible insomnia, and/or excessive daytime sleepiness (EDS). Many adjectives have been used to describe this RLS feeling, i.e., “like a bag of worms,” etc. I have attached a chart of the international diagnostic criteria to confuse you further (Table I). But the pneumonic URGE is a simple approach and incorporates the international diagnostic criteria. Urge to move, Rest makes it worse, Getting up and moving makes it better, and Evenings are the worse.

I think sometimes what is easiest is to state what RLS is not. It is not peripheral neuropathy, which is present 24/7. However, many people that have peripheral neuropathy can have RLS as well. It is not nocturnal leg cramps which are those “charlie horses” that “draw up” on an individual in the middle of the night
and make them jump out of bed. RLS is not claudication, where people complain of “pain” in the legs with walking, relieved by rest, but in severe cases made worse by elevating the legs in bed. RLS is not varicose veins, even though there are some reports that treating those varicosities can make 1/3 of RLS sufferers better. RLS is not “sleep starts” which are the sudden “jerks” that one might experience after a long hard day when one is drifting off to sleep. Sleep starts are usually few in number and are more truncal or nuchal in their movement and not in the legs. But most importantly, RLS is not everyone that kicks his or her legs at night. This is where the mistakes are made. Many important sleep disorders which are more important than RLS, yes more important, are associated with an arousal maneuver of kicking one’s legs.

The most important syndrome that is not RLS is that of sleep disordered breathing (SDB) or sleep apnea. As people obstruct their airway with sleep apneas at night, they will have oxygen desaturation, and in turn as part of the fight or flight mechanism, kick their legs or “sleep restlessly” in order to arouse themselves from sleep so that they can start breathing again. The treatment of the legs with all the Requip in the world will not open their airway. These “kicks” many times will be scored on sleep studies as periodic leg movements (PLMS) and one might want to make the assumption that PLMS are RLS, but they are not. 80 to 90 percent of people with RLS will have PLMS. But importantly, only 30 percent of individuals with PLMS will have RLS. And some report as high as 30 percent of all studies will have PLMS. I see PLMS daily in sleep studies for sleep apnea, and daily I see them go away with treatment of the airway obstruction.

IMPORTANT. RLS should be diagnosed before patients go to sleep. If their complaint starts after they go to sleep, there is a 70 percent chance that they have something else and most likely you are missing sleep apnea which has greater long term consequences.

Restless Leg Syndrome comes in two flavors. Primary or
idiopathic, and secondary. Primary is a diagnosis of exclusion. In other words, I have ruled out all the secondary causes. Primary has a bunch of new genetic information about it. It is autosomal dominant with strong family history and has a whole set of alphabet soup of chromosomal abnormalities that you could memorize to impress your friends. A single variant in the BTBD9 gene on chromosome 6 contributes to 50 percent of the population risk. Importantly, this genetic work shows that an autosomal inheritance can affect children at very young ages. It is now clear that the pendulum of diagnosing every kid that did not do exactly as his or her teacher said as attention deficit hyperactive disorder (ADHD) might be over done. And that some of these kids are sleep deprived from cases of sleep apnea and restless leg syndrome. These cases need to be recognized, but for humanity sake, not become the next Lyme's disease, chronic fatigue syndrome, or ADHD. Again, these last three diagnosis are REAL and important diseases, but like RLS, without confirmatory tests, can easily be over diagnosed and abused as well as under diagnosed.

Secondary RLS is where I would hope that you would focus your attention. The pathophysiology of RLS is not completely worked out and much of it is heretical, or found by trial and error. But it is clear that there is an iron and dopamine link. The dopamine receptor (DA) is associated with many diseases and the best that I can tell, has at least five subtypes. Four diseases that are associated with this receptor are RLS, Parkinson’s disease, schizophrenia, and bipolar and none of them appear to predispose each other at this time. Iron is a co-factor for tyrosine hydroxylase, and is the rate limiting enzyme for dopamine synthesis. The theory of over-stimulation or over-functioning of the DA receptor complex versus under expression of this receptor maybe felt to have some role in these diseases. But it remains unclear. What is clear is that the agonist of the D2 and D3 receptor make RLS better and antagonizing them, or of the serotonin receptor complexes, can
make some these patients susceptible to RLS manifest their disease, or make those with RLS worse.

What is important to remember is that iron deficiency can either lead to, or unmask cases of RLS. And dopamine stimulation makes it better, even those with iron deficiency. If you can remember this small bit of pathophysiology, you can deduce secondary causes (Table II) and complicating drugs (Table III). Many anecdotal stories of middle-aged people who developed RLS were ultimately found to be iron deficient. They were then worked up for their iron deficiency anemia, found to have early stage colon cancers, and were resected. A year later, they were without RLS and alive and well.

In the summary, I have listed an over kill battery of lab tests that may or may not ultimately have anything to do with RLS, but may take you in the right direction anyway. The most important are the iron studies. Many advocate simply for a ferritin, and if greater than 50, it is “ok.” I still think an iron, TIBC, plus the ferritin will lead to less misses.

Treatment

The first step to treating RLS is backing up and making sure that what you are treating is a before sleep syndrome. If it is an after sleep onset, send them for a sleep study. Make sure they don’t have secondary RLS and if they do, work them up and treat that. Next, look at your medicine list and ask if there is something there you can change or withdraw that might be aggravating the syndrome. We have all seen cases of SSRI’s that aggravated RLS. Unfortunately, so can the tricyclics. Then ask yourself and the patient, is it bad enough to treat with an expensive medicine that can have plenty of side effects? I have listed the numerous “touchy feely” holistic remedies that have been championed. As long as the harm is low and the disease is mild, it is probably reasonable to try some of these if the patient prefers.
If the patient has moderate or severe disease, then you need to treat with a dopamine agonist, i.e. Mirapex (Pramipexole) or Requip (Ropinirole). These drugs are effective in 80 to 90 percent of cases. I would strongly suggest, if a low to moderate dose of these meds do not make a dramatic difference in your patient, that you might have the wrong diagnosis. It is time to consider starting over, and/or getting a sleep consultation, and a sleep study of good quality. But remember the vast majority of people will be helped substantially with small or homeopathic doses of these medicines. Start low and go slow. That is a big secret to success with these agents.

Treatment with the dopamine agonist group is associated with numerous side effects especially in the parkinsonian group where higher doses are required. Studies of RLS sufferers have shown lower side effects, but probably because of lower doses. Still, the side effects are significant and need to be monitored. Again, I have attached a list of commonly known side effects, but importantly, some rare side effects that can be very severe (Table IV). New side effects are growing over time.

Augmentation is an unusual but significant long term complication of treatment of this disease. It is seen more with Sinemet (levodopa) and estimated at 82 percent and hence this drug has been relocated to the treatment of intermittent RLS (less than three doses per week). What occurs with augmentation is that over time, the symptoms of RLS creep into the day and perhaps into the arms. Drug escalation is usually tried unaware of augmentation, and may be successful for a while, but ultimately withdrawal and/or drug holidays are paramount. If not recognized, this can really lead to significant complications. The other dopamine agonists are found less often to have this side effect (20-30 percent), but time will define this better.

I have listed the alternative drugs to treating RLS in the handout. But I would highly caution you on the use and overuse of narcotic analgia, antiepileptics, and the benzodiazepines
(clonazapam). If daytime hypersomulence was one of the reasons you were treating, you might be defeating your purpose because of the hangover affect that many of these mediations can cause. Additionally as a pulmonologist, we are seeing the down stream effect of long-term narcotic analgia in non-terminal diseases. I am seeing cases of recurrent and chronic pneumonia, unexplained bronchiectasis, and poor functioning quality of life with these drugs. Additionally, increasing numbers of central sleep apnea are seen in these patients in the sleep lab.

I have attached an algorithmic approach with tables of lists to consider next to it. I am not the first to write a similar algorithm, and many similarities can be seen from other reviews. Additionally, it will not be the answer for all cases, but my hope is that the “90 Percent Rule” will be served.

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American Board of Internal Medicine, Pulmonary Medicine, Critical Care Medicine, and Sleep Medicine
Text


American Academy of Sleep Medicine, *International Classification of Sleep Disorders, 2nd Edition: Diagnostic and Coding Manual.* Westcheser, Illinois: American Academy of Sleep Medicine, 2005. *This is one of the “bibles” of Sleep and is standardly memorized cover to cover for the Sleep Boards. It has a lot of good information but reads like a coding/classification manual.*

Review Articles

*RLS has become such a rapidly growing topic you will find excellent reviews in almost every discipline.*


Uptodate.com. *Has an excellent review as well.*
“An Update on the Dopaminergie Treatment of RLS,” Sleep Medicine 2003, 4(2)101-119. *This is the second of two and the latest “practice parameter” review as released by the Society of Sleep Medicine. A little dated but still a fine review of the meds.*

**Articles**

Treatment of RLS

**International Diagnostic Criteria**

**Diagnostic Features**
1. An Urge to Move the Legs
   Usually Caused by an Uncomfortable or Unpleasant Sensation
2. The Urge to Move is Made Worse with Rest
3. The Urge to Move or Sensation is Made Better with Movement
4. The Urge to Move or Unpleasant Sensation is Worse at Night

**Supportive Clinical Features**
1. Positive Family History
2. Positive Response to Dopaminergic Agents
3. Presences of Periodic Leg Movements (Awake or Asleep)

**Associated Features of RLS**
1. Variable Course, Progressive
2. Normal Physical Exam
3. Sleep Disturbance is Common

**Secondary Causes of RLS**
1. Iron Deficiency
2. End Stage Renal Disease
3. Pregnancy
4. Parkinson’s Disease
5. Rheumatoid Arthritis
6. Charcot-Marie-Tooth Type II
7. Spinal Cerebellar Atrophy
8. Spinal Stenosis
9. Venous Insufficiency
### Table 3

<table>
<thead>
<tr>
<th>Complicating Drugs of RLS</th>
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<tbody>
<tr>
<td>1. SSRI’s [Fluoxetine, Paroxetine, Sertraline, Remeron (8%)]</td>
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<tr>
<td>2. Tricyclics (Amitriptyline)</td>
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<tr>
<td>3. Antihistamines</td>
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<tr>
<td>4. Dopamine Antagonist (Metaclopramide, Respedone, Clozapine, Antipsychotics)</td>
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### Table 4

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<tr>
<th>Dopaminergic Drug Side Effects</th>
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<tbody>
<tr>
<td>1. Sleepiness, Light Headedness, Ataxia</td>
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<tr>
<td>2. Nausea and GI Upset</td>
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<tr>
<td>3. Sleep Attacks, Uncontrolled Falling Asleep Reminiscent of Narcolepsy and Cataplexy</td>
</tr>
<tr>
<td>4. Augmentation or a Worsening and Escalation of Symptoms</td>
</tr>
<tr>
<td>5. Compulsive Personality with Excessive Gambling, High Risk Sexual Activities, and Other Compulsive Traits</td>
</tr>
<tr>
<td>6. Increase Suicide Risk</td>
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<tr>
<td>7. Numerous Other 1 to 10 Percent Complaints</td>
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### Table 5

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<th>Dopamine Agonist</th>
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<tbody>
<tr>
<td>1. Pramipexole (Mirapex) 0.125mg Start and May Escalate Up to 1.5 mg Divided in 2-3 Daily Doses (Never go above 0.5mg)</td>
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<tr>
<td>• I Start With Half the Starting Dose in the Elderly</td>
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<tr>
<td>• Same Dose for 3-4 Days or Longer (Week)</td>
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<tr>
<td>• I Shoot for 70% “Wow, I am much better doc, not perfect, but I could live with this.”</td>
</tr>
<tr>
<td>• Must Give 2 Hours Before Sleep Period Secondary to the Onset of Action</td>
</tr>
<tr>
<td>2. Ropinirole (Requip) 0.25mg Start and May Escalate to 3 mg Divided Over 3 Doses</td>
</tr>
<tr>
<td>• Classic is 0.25 to 0.5 After Two Days, Then Double in One Week. I go slower than that, and make all changes in a one week interval.</td>
</tr>
<tr>
<td>• It is like hypertensive medicines with their high total dose rate. I have never seen them be that effective if you went to some huge dose. Just every side effect.</td>
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THE COMMON PARASOMNIAS

Parasomnia simply means “around sleep.” The phrase “things that go bump in the night” was coined by some author long lost to me, but it gives a good visual description of parasomnias. I think of parasomnias as undesirable activities that are caught somewhere in that world between Awake and Asleep.

The notion that the brain, as related to sleep, is homogenous and like a rheostat or dimmer switch that simply dims to off is a misnomer. The brain is incredibly compartmentalized. It has multiple compartments doing varying activities during the three states of “being” (awake, rapid eye movement [REM] sleep, and non-REM sleep). As we nightly measure brain wave activities in a sleep lab, it becomes clear that the brain is almost constantly jumping between these levels of consciousness and all of these “compartments” are trying to “stay in suite.” Parasomnia is when one of these “compartments” is in a different stage of being then the rest of the brain. For example, in sleepwalking we have the intrusion of the motor cortex into deep non-REM slow wave sleep. Or we can have motor activity intrude into REM sleep and hence, REM Behavior Disorder. Or we can have the animal basic drives intrude into sleep as in sleep sex or sleep-related eating disorder. Or we can work the other way around and have the intrusion of sleep into wake. This is exemplified by micro sleep or automatic behavior where a driver may pass his turn off exit and have no recall of that, yet he was driving just fine. Or the classic “I wasn’t asleep” when someone is unaware he fell asleep while talking to you. More pathologic examples are narcolepsy where one can literally have REM sleep intrude into wake to cause cataplexy. With this “passing out” of cataplexy, one looses total control of the body to the paralysis of REM sleep yet is totally aware of his surroundings. Hypnogogic hallucinations is when one sees or hears things at sleep onset which are felt to be REM sleep (dreams) jumping into consciousness at bed time or sleep onset.

The classification of the parasomnia has become almost intuitive. It is classified by what stage of sleep you were in and
what you were doing at the time. So non-REM or REM sleep disorders and if it is not clear which, they put you in the “other” category.

The International Classification of Sleep Disorders
American Academy of Sleep Medicine

Disorders of Arousals (Non-REM Sleep)
- Confusional Arousal Disorder
- Sleep Walking
- Sleep terrors

Parasomnias of REM Sleep
- REM Behavior Disorder
- Recurrent Sleep Paralysis
- Nightmare Disorder

“Other” Parasomnias
- Sleep Related Disassociated Disorder
- Enuresis (Bed Wetting)
- Groaning (Catathrenia)
- Exploding Head Syndrome (Hearing Loud Bangs in Sleep)
- Sleep Related Hallucinations
- Sleep Related Eating Disorder
- Other

If you think about it, the classification is pretty arbitrary and in clinical practice there is a lot of blurring of the lines in their appearance. And it is not coincidence that many of these syndromes respond to the exact same therapy.

REM SLEEP BEHAVIOR DISORDER (RBD)
I think as a physician that takes care of adults, RBD is probably the most important and most common parasomnia you will see. For the uninitiated, you have probably lumped this syndrome into your “sundowners” category. These are the old guys, pre- or para-Parkinson’s disease, that lie in bed after being fine all day but then act out their dreams, pick at the air, or in the extreme cases, get up and tackle the dresser which turned out not to be a running back. Or worse, punch their wives and cause severe injuries as they dream of historic Mohammed Ali fights. In simple terms, it is the loss of the inhibition of muscle movements that we all have during REM sleep so we don’t do exactly that and act out our dreams.

The classic presentation of RBD is the older man with sleep injuries (80%) or he or his spouse reports acting out dreams (90%) and sleep disturbance (20%). I personally believe RBD is far more common than the above study reports. When a man is “picking at the air” in sleep or punches and causes no injury, either it is not reported to the physician or it is not bad enough for their physician to seek advice from a sleep specialist. As I personally have become more aware of this syndrome, it becomes clear as I walk around the hospital at night, the number of cases of mild RBD that are lumped into “sundowning.”

Predisposing factors to RBD have quoted 50-60% as idiopathic but recent observations and data suggest that it is a precursor to Parkinson’s disease in most. And if you follow them long enough, more than 75% will develop Parkinson’s. However, other neurologic diseases, tumors, strokes, bleeds have predisposed to RBD and it has been described in narcolepsy.

Like RLS, many drugs have been shown to unmask or bring out REM behavior disorder. Easy to memorize, many of the drugs are the same that bring out RLS. The drugs are SSRI’s (by adding
or withdrawing these drugs, it can cause REM rebound, i.e., more REM sleep, and hence more opportunity to go into RBD), caffeine, MAOI, anticholinergics, withdrawal of alcohol, or benzodiazapine and can all do similar effects on REM. Additionally, sleep deprivation can bring out REM sleep and in turn RBD.

The pathophysiology is unknown but needless to say, with the association of Parkinson’s disease, there is a lot of interest in dopamine and the substantia nigrae.

The diagnosis of RBD is simply a sophisticated sleep study that shows REM sleep without the loss of motor inhibition. It sounds great on paper, I only wish it was that simple. Unless the case is florid, it can be a difficult read at best. Video monitoring is a must. Additional evaluation of obviously a good neurologic exam and MRI of the head are not uncommonly done by the time they are seen in a sleep lab. And a case-by-case analysis would be important for additional evaluation.

The differential diagnosis of RBD for the most part includes confusional arousal disorder, sleepwalking, and nocturnal seizures. Sleep walking tends to be in the younger individual with a childhood history, occurs earlier in the night (during non-REM slow wave sleep), with eyes open, and the activities tend to be more organized like walking around the house, outside, etc., but the individual rarely remembers the event. RBD tends to be in early morning hours (more REM cycles), in older guys, with eyes closed, more violent, less complex activities, quicker out of bed and hitting the dresser or punching, and many recall dreaming and awaken quickly from the event. They rarely, if ever, leave the room (unless it’s through the window – ouch).

Nocturnal seizures are always in the differential diagnosis. These tend to have more stereotypic movements that are repetitive. Many are frontal lobe and hard to diagnose. Seizures during the day are great hints. (But rarely a frontal lobe seizure can present as walking around at night and then be very difficult to discern from
RBD or sleepwalking.) Punt these then to neurology or a very sophisticated sleep physician, not to me! They require very sophisticated EEG monitoring that does NOT occur in most sleep labs.

Confusional arousal disorder is discussed below and finally, psychiatrics. Good luck.

For all these disorders, the triggers seem to be a common theme. Set the right milieu or background as outline above and then apply a loud noise, sleep apnic arousal, or some other stimulation, and BOOM. One part of the brain turns on, another part is asleep, and you have a parasomnia.

The treatment of RBD is pretty straightforward. Remove the SSRI, MAOI, sleep deprivation, and alcohol. Use “sleep safety” by preparing the room for combat and setting the bed away from the second floor window so one does not get hurt. Use of a low dose of clonazapam works in 90% of patients. Alternative drugs such as melatonin, carbamazapine, gabapentin, imipraimine, and other trycyclics have been reported, but if you get to here, dump them to a neurologist or a sleep specialist, NOT TO ME!

**CONFUSIONAL AROUSAL DISORDER**

Confusional arousal disorder can be confusing to diagnose and is similar to RBD and other parasomnias. This probably occurs coming out of NREM sleep, is more violent than many parasomnias but seems to be shorter lived than sleepwalking. My impressions are it last seconds to a minute and is well described with the trigger of sleep apnea. The few cases I have seen have always been around sleep apnea, alcohol, or sleep deprivation. I, like others, have “cured” this by treating the sleep apnea (eliminating the trigger of arousal), discontinuing alcohol, and improving sleep hygiene (changing the milieu), and then seeing no further episodes after that. I would highly suggest you send these to a sleep specialist.
SLEEPWALKING

Sleepwalking is very common in childhood (40%) but extends into adult life in up to 2%-4% of people. The overlap again with other arousal disorders is common and confusing. These can be rare and mild/calm or be frequent and violent and long. Sleep deprivation, alcohol, sleep apnea, illness, many drugs (psychotropics, antihistamines with stimulants, lithium, benzodiazapines [big press with Ambien], street drugs), and emotional stress can all act as triggers for the resurgence of sleepwalking.

Treatment centers around good sleep hygiene, avoidance of inciting drugs, removal of any triggers (external - loud noises or internal - sleep apnea), creating a safe and secure environment, gently redirecting to bed if up walking, and rarely prescribing medication. When medication is used clonazepam is the most commonly prescribed. If you get to this point, I would send them to a sophisticated sleep center and again not to me.

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