Overview
This educational book contains a series of 17 case studies in psychiatric disorders, all adapted from real practice, that provide a look into how cases look like after initial assessment and over time, identifying the treatments that work, the treatments that do not work, the mistakes, and the lessons to be learned.

Target audience
This book has been written in six chapters that have been developed for clinicians who are specialists in psychopharmacology. The last chapter focuses on future directions in the treatment of psychiatric illnesses.

Statement of need
- Bipolar spectrum disorders are highly prevalent and carry a substantial burden that is improved through medication treatment. Unfortunately, many patients with bipolar disorders do not receive treatment or receive suboptimal treatment.
- Bipolar disorders commonly occur co-morbidly with other psychiatric illnesses complicating treatment
- In order to improve outcomes for patients with psychiatric disorders, this educational book is designed to improve clinician performance with respect to the treatment of bipolar disorders.
- There are available diagnostic strategies that can aid in the treatment of people with bipolar spectrum disorders
- There are effective clinical strategies for the monitoring and treating psychiatric mood disordered patients.

Learning objectives:
After studying the material the participant should be able to:
1. Recognize the importance of using the lowest possible effective dose of atypical antipsychotics used in augmentation of mood stabilizer medications in cycling mood disorders
2. Demonstrate the use of a self rating scale to monitor orbito frontal cortex (OFC) and dorso lateral prefrontal cortex (DLPFC) symptoms in people with cycling moods
3. List cognitive side effects secondary to mood stabilizers
4. Differentiate between cognitive symptoms secondary to illness vs. cognitive side effects secondary to mood stabilizer medications
5. Identify the best atypical augmentation strategy for mood stabilizers in different medical conditions
6. Discuss dose reduction strategies using a risk vs. benefits medication chart for mood stabilizers after augmentation with atypical antipsychotics
7. Explain the utility of a test dose of Abilify at 10mg using a self rating scale
8. Discuss the different conditions under which low and high dose Abilify, a dopamine partial agonist, are used
9. Analyze changes in symptom frequency and severity on a self rating scale in response to an Abilify10mg test dose

Dr. David R. Torres has does not have any disclosures, pharmaceutical affiliations or stock holdings to report.

Preface 2
Introduction 4
Chapter One 7
Understanding and Measuring symptoms
Managing medications in people whose moods cycle
The Cycling Mood Rating Scale (CMRS)
How to quickly assess brain functioning in an emergency situation
How does a cognitive self rating scale guide medication management?
The basic principles of medication management using a self rating scale
The orbito frontal subscale
The meso cortical memory subscale
The dorso lateral prefrontal cortex subscale
The Cerebellar subscale
The Executive functioning subscale
The Motivation and fatigue subscale
Diagnostic labels
Remission – getting completely well should not be a challenge
Resilience
Sleep and recovery
Energy and the four dopamine pathways of pain and pleasure
Anxiety and pain
Racing thoughts and irritability

Chapter Two 29
Psychopharmacology in psychiatric practice
Which drug to use first?
The test dose
The Abilify partial agonist story
Abilify dosing during the study
Abilify is a multifunctional drug
How to use the CMRS to reduce medications
Signal to noise ratio
How to manage a cycling mood state with Abilify
How to treat bipolar depression
The CMRS and tracking symptoms
The CMRS
The test dose and the CMRS
The clinical interview
Poly pharmacy
Medications risks vs. benefits medication reduction chart
Using the CMRS with atypical antipsychotic treatment strategies
Functional outcomes
Bipolar disorder in family practice
How to use Abilify and Geodon in diabetic patients in augmentation
with antidepressants
Treatment resistant depression

Chapter Three
The care of bipolar patients
How to treat bipolar depression
*Case studies

Chapter Four
Future directions
Schizophrenia
Bipolar disorder
The unmet need; the treatment of acutely suicidal people
Intelligence – what happens next?

Appendix A, B, C, D, E

References
atypical antipsychotic medications. This efficiency or improvement in functioning may be a result of synaptogenesis, the creation of new synapses in the brain and neurogenesis, the creation of stem cells differentiating into new neurons in the hippocampus and probably the olfactory bulb.

Abilify is a long acting dopamine partial agonist and atypical antipsychotic medication. It acts as a 5HT1A partial agonist and it is a 5HT2A antagonist by increasing dopamine release in the prefrontal cortex, tuberoinfundibular pathway and meso cortical pathways.

Abilify has both anti anxiety and energizing properties at low doses below 5 mg daily and at higher doses above 10mg a day, it functions as an antagonist. It is best described as a multifunctional drug which functions very differently at different doses and is a complicated medicine to use in combination with other medications especially when used in the treatment of people who have bipolar depression. The cases I have treated over the last 20 years in private practice have given me insight into how to use this dopamine partial agonist at both D2 and D3 receptors at varying doses to treat many facets of emotional challenges people have and have led to the development of a rating scale specially designed to treat and manage medications in people who have cycling mood disorders. Over the last two decades, our understanding of how to treat bipolar depression has changed. Clinicians understand that antidepressant treatment should be used in a limited fashion if at all in bipolar people and it is preferable to use 2 mood stabilizers one that promotes energy and one that promotes sleep to stabilize mood swings instead of an antidepressant. People with excessive mood swings have an illness that manifests as fluctuations in level of motivation probably as a result of aberrant firing of dopamine releasing neurons in multiple pathways.

As new treatment strategies emerge, a careful assessment of the risks vs. benefits associated with use of all medications needs to be performed and rating scales will be a part of this assessment. There will be a greater tendency to look at the newer atypical antipsychotics as first line treatment as they are less likely to cause cognitive dysfunction, birth defects in woman of child bearing age and now may have fewer metabolic risks than their predecessors. Prescribing atypical antipsychotic medications which work through g-protein mediated receptors is an art as optimal dosing of these medications is variable from person to person. Many of the mood stabilizers work directly on voltage gated ion channels and rapidly effect ion flow across nerve membranes making cognition challenges more frequent at higher doses. It is important to use medications at the lowest possible effective dose which can minimize the risk of potential side effects and a carefully designed validated self rating scale is offered to facilitate the art and theory of medication management of mood disorders

Introduction

The standard treatments for bipolar disorder are Lithium, Depakote, Tegretol and the atypical antipsychotics. Many people who have co -morbid medical challenges such as closed head injury and exposure to toxic levels of alcohol in the past may be sensitive to the atypical antipsychotics at usual recommend doses when used in augmentation of mood stabilizers. The objective of this case study was to evaluate mood stability after low dose atypical antipsychotic augmentation of mood stabilizers in 17 bipolar people using a brief cognition screen and the Hamilton depression scale. People with bipolar one and two disorder who have been stable psychiatrically in an outpatient private practice for 2 to 20 years were used in the study. These people had subtle signs of toxicity on average doses of mood stabilizers. Previous attempts to reduce cognitive...
imparing mood stabilizers were not tolerated as mood instability and depression recurred. Low dose Abilify at 2mg ¼ tablet augmentation enabled dose reductions of lithium, Tegretol and Depakote without mood instability or depression over three years. A clinical scale called the COLORADO Mood Rating Scale (CMRS) was developed specifically for the purpose of bipolar medication management by evaluating neural circuit functioning.

In my case series, low dose Abilify, Geodon, Saphris and Latuda augmentation appeared to have a modest energizing action and prevented recurrence of symptoms of depression enabling dose reductions of mood stabilizers by about 25% and stopping Depakote in one case. None of the people in the case series required hospitalization and remained in remission from depression. Many of the people included in the case series were intolerant of usual doses of sedating atypical antipsychotics. Quantifiable improvements in cognition were noted in all people as a likely result of reduction of mood stabilizer levels although improvement in attention due to Abilify itself could not be ruled out. A functional improvement in the quality of life was also noted in study subjects.

Many of the patients in the cases described in the book started my practice in 1992. Over the years, many algorithms have been developed to treat bipolar depression in people with cycling mood disorders and the atypical antipsychotic treatments at that time sometimes left people at cardio-metabolic risk. For many of my people, the risk of potential cardiovascular disease was too great for a trial on Zyprexa/Prozac or Seroquel XR or Seroquel IR. Lamictal did change my practice, however, as it did for many of my colleagues as this medication provided many people with cycling moods and low energy states with long hoped for energy. Abilify has received 15 FDA indications for the treatment of psychiatric conditions. This medication works through a unique partial agonist dopamine mediated mechanism of action and does not seem to cause a significant risk of future metabolic syndrome as compared to other atypical antipsychotics. Abilify was a logical next step that needed to be tried on the people in my practice who were having cognitive challenges as a result of utilizing higher doses of mood stabilizer medications to stabilize their mood. While the FDA guidelines are very specific regarding dosing, I found initially that many of my people were intolerant of the FDA recommended doses of the standard atypical antipsychotics probably as a result of pre-existing head injuries and gliosis resulting in abnormalities of their glutamate system. Some had past alcohol related brain toxicity requiring me to start using lower doses of the medication. Thus, I started using the lowest possible dose I could start with in my people by breaking Abilify 2mg into ¼ tablets. While I had initially intended to increase the dose of Abilify into the FDA recommended ranges, I quickly found out in my case series using the COLORADO Mood Rating Scale (CMRS) that as an add on strategy, low dose Abilify below 5mg could stabilize moods and at least partially provide energy to people in low energy states as an augmentation strategy. In order to monitor progress, I continued to use the COLORADO Mood Rating Scale (CMRS) a self rating scale verified by a third party to guide medication management. The CMRS looks at three major brain circuits and guides medication management of atypical antipsychotics and mood stabilizers. Clinicians know that severity and frequency of symptoms guide choice and dosing of the medications and side effects guide dose reduction of a mood stabilizer after an augmenting atypical is added over the course of several months.

During periods of de-compensation in my people or some patients who engaged in drug misuse of stimulant medications, I learned that a one time in office test dose of Abilify at 10mg could avert a hospitalization and its effect would last for about 3 days as reported on a validated self rating scale. The self rating scale was created based on both FMRI and EEG studies in neuroscience.
and our current understanding of neural circuits to monitor symptoms and adjust medications in people with cycling moods. Over time, it became apparent to me that patterns on the COLORADO Mood Rating Scale (CMRS) could be a guide to medication management and predict a response to medications particularly atypical antipsychotics. Medication response to the atypical antipsychotics is more predictable provided the rating scale was validated by an accompanying person, if I had enough clinical data regarding past treatment response to medications and medical history. I am now being asked to treat the children of the patients in the study requiring closer scrutiny of symptoms and their response to low dose atypical antipsychotic medications. Depression is seen ubiquitously in family practice. In family practice clinics, the SNRIs treat the symptoms of depression which may also include pain, anxiety and vasomotor problems. Thus, co-morbidities are more the rule than the exception in family practice. Although many of the people will improve with a single antidepressant trial, many will not and many who have a cycling mood illness may get worse. In order to effectively treat depression and possibly reverse the underlying mechanisms that make people who suffer from mental illness dysfunctional, requires that we treat someone to sustained remission as quickly as possible. We no longer wait the usual 4 to 6 weeks for a trial of an antidepressant medication to end before starting an augmentation strategy or switching medications. We now know that a SSRI will have its greatest effect within the first 2 weeks and if the effect levels off augmentation is quickly considered. This book is designed to help those who seek to help others who present with depression, anxiety and co-morbid disorders. Many times the people we see in practice have a colorful family history or a colorful history of drug misuse and use of an antidepressant may place someone at risk of having a cycling mood. We know that the number needed to treat (NNT) with antidepressants changes from preschoolers to adolescents to elders making a risks vs. benefits assessment an ongoing challenge. The number needed to harm in adolescents is 1 in about 112 meaning that the risk of someone on antidepressants developing mania or increasing suicidal thoughts can occur in about 1 in 112 patients. The number needed to treat using antidepressants in adolescents is 1 in 8 so we know that we will help 1 kid in 8 using antidepressants and we also know that many of them will do well on their own and with cognitive behavioral therapy. It is the objective of this book to provide you with information and facts to help you think about how you can improve specific cognitive abilities in the people you see who may be having sleep, energy, or anxiety challenges. This book will give you some practical advice you can put to good use immediately. Many of the points raised in this book come from our current understanding of neuroscience through FMRI and PET scanning studies. Many of the medications mentioned may work through improving neural circuit efficiency. Often, medications may work by improving focused attention to allow the brain to heal itself through neuroplasiticy and possibly neurogenesis. Through case examples from my practice, this book discusses the use of pharmaceutical medications currently available and some that are in development. The medications discussed are designed to treat illness though functional improvement in some people may occur in the form of improved processing speed. The benefits of long term stability of symptoms are seen in the form of improved, work, home, and relationship functioning. Attaining remission or an absence of symptoms is everything as we may be able to reverse pathology when people are in remission from their illnesses. Attaining remission becomes easier measuring functional outcomes using a simple self rating scale. It is the objective of this book to provide you with information and facts you need to help the people you treat improve specific cognitive abilities while being treated for challenges they may be having with sleep, energy, or anxiety. The Art and Theory of Bipolar Disorder Medication Management is designed to be easy to read, innovative, informative and instructive in getting the
best results using psychotropic medications. There will be facts as well as perspectives addressed. I am hopeful that this book will teach and motivate you to think about your treatment of people with bipolar mood disorders and enable you to help your people and their children to live long and productive lives.

Chapter One
Understanding and measuring symptoms

Managing symptoms in people who have a cycling mood disorder

70% of people who have a cycling mood disorder have many co-morbid conditions and require at least two medications to manage their illness. One of the medications is a medication that promotes energy and another medication can be used to promote sleep. In this way, an antidepressant medication in bipolar people can be stopped abruptly except for those that have discontinuation associated with them like Paxil and Effexor. Quantifying symptoms based on severity and frequency of occurrence can help decide which medication to use first in a person. There are 3 major circuits in the brain which are associated with different symptoms which can be used to guide medication management. The first circuit is the orbito frontal circuit which guides emotional control. The second circuit guides attention and focus, and the third circuit involves the cerebellum which is responsible for coordinating our thoughts and actions and can be used to assess the possible toxicity of mood stabilizer medications.

1. MEDIAL frontal cortex (OFC) – emotional control
2. Dorsal lateral prefrontal cortex (DLPFC) – attention, concentration and negative symptoms (attunement)
3. Cerebellar pathways – motor and thought coordination – can be used to determine mood stabilizer dose reduction after an atypical antipsychotic is used as augmentation therapy

The COLORADO Mood Rating scale is a 60 question self rating scale designed to document a need for treatment with medications and assess symptoms and neural circuit inefficiency for treatment. The scale was designed for medication management as many people with bipolar disorder may have many co-morbid conditions. The validity of the scale increases with a comparison with an observer rated scale and the self reflect scale. There are many free clinical scales on the web and the CMRS is a composite of several assessment scales. There is a subscale in the CMRS specifically designed to look at cerebellar functioning which is useful clinically when a dose reduction of mood stabilizers is required or a switch to another atypical antipsychotic occurs. The scale raises the bar on assessing cognitive functioning so that improvement in executive functioning or planning is the ultimate goal once remission occurs. The CMRS is reviewed systematically and does not replace the clinical interview. Rating scales can save a physician time by eliciting specific information which enables a provider to ask more direct questions. After a clinician uses the rating scale for a while, symptom patterns can be easily seen which are amenable to certain types of drug treatment.
The CMRS prioritizes symptoms in a functional order. First we look at functioning, then MEDIAL frontal circuits second, then dorso lateral prefrontal circuits next. Cerebellar functioning is assessed next and the person's self assessment of their executive functioning or ability to plan is done last. By reviewing neural circuitry in this systematic fashion, a medication treatment plan can be started and a general improvement in functioning can occur and improved job performance can result. The major idea is that untoward behaviors need to be addressed first by treating orbito frontal pathway dysfunction to make this pathway more efficient. Getting rapid control of out of control behavior is where medication management shines and is most useful. The specific core symptoms of sleep, energy, anxiety, racing thoughts and irritability need to be assessed and treated effectively. Second, attention to the dorso lateral prefrontal cortical pathways needs to be addressed. These circuits enable focused attention and concentration which are directly related to optimal work performance. Cerebellar functioning and coordination should then be assessed and managed. Finally, executive functioning or the ability to plan for the future can then occur. Severe symptoms on the CMRS that are occurring more than 50% of the time typically requires medication management if standard therapy and basic self care are not able to optimize functioning acutely. The CMRS was specifically designed for people who have a cycling mood disorder that requires treatment with multiple medications but it can be used by others.

How to quickly assess brain circuits in an emergency situation
The CMRS enables a provider with a means to assess brain functioning quickly through symptom patterns and easily assess which medications are most likely to help someone acutely. The rating scale prioritizes functioning and documents a need to treat. MEDIAL frontal circuit functioning is next assessed and if needed, a serotonin dopamine antagonist or dopamine partial agonist may be used. Once these circuits are stabilized then the DLPFC circuits or circuits responsible for cognition and negative symptoms are addressed. Dorso lateral prefrontal circuit inefficiency can be improved with stimulants, non-stimulants and wake promoters. Side effects from other medications are reviewed on the cerebellar subscales and medical problems are noted on the fatigue subscale. Finally executive functioning or planning is the last subscale to be assessed.

How does a cognitive rating scale guide medication management?
Pattern recognition is something humans excel at and is the bane of computer programmers seeking to develop a computer model for visual object recognition. The brain learns to identify objects by learning in a hierarchal manner and we can learn medication management the same way by understanding brain neural circuitry and prioritizing which pathways need to be regulated first then secondarily.

Three basic principles of medication management using a validated CMRS self rating scale:
• MEDIAL frontal circuit deregulation is best treated by atypical antipsychotics e.g. Abilify, Geodon, Saphris, Latuda, and Fanapt with care given to understanding severity, frequency of symptoms and co-morbid medical problems like closed head injury and other neurologic problems.
High energy mood states require higher dosing of an atypical antipsychotic partial agonist and low energy mood states typically require lower doses. The more frequent and severe the symptoms on the CMRS are, generally higher dosing of atypical antipsychotics are needed as a first start.
• **Dorso lateral prefrontal** cortex deregulation is associated with challenges performing calculations and low motivation. These symptoms are best treated after orbito frontal circuits are stabilized and are treated with stimulants, wake promoters, Guanfacine ER or atomoxetine. The negative symptoms of schizophrenia manifest by challenges in this pathway. More frequent symptoms on the CMRS generally require higher dosing.

• **Cerebellar symptoms** on the CMRS may be the result of mood stabilizer treatment at high doses and can worsen months after starting augmentation with Abilify, Geodon, Latuda, Fanapt and Saphris and other atypical antipsychotics requiring reduction in the original mood stabilizer dose. Neurologic illnesses may also be represented by elevations in this pathway. Signs of toxicity on anti seizure mood stabilizers include head ache, blurred vision, double vision, coordination problems and fatigue.

---

<table>
<thead>
<tr>
<th>MEDIAL frontal circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Abilify, Geodon, Saphris, Latuda, Fanapt</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dorso lateral prefrontal circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stimulants, wake promoters, Guanfacine ER or atomoxetine.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cerebellar side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Headache, blurred vision, double vision, coordination problems and fatigue.</td>
</tr>
<tr>
<td>- Dose reduction of mood stabilizer Depakote, Lithium, Tegretol, Trileptal, and other antiseizures</td>
</tr>
</tbody>
</table>

**Examples:**

MEDIAL Functioning circuit disruption 100% of the time:
- May be indicative of severe mood, anxiety, impulse control disorders, chronic and acute psychotic disorders requiring treatment with antipsychotic agents first with the lowest risk of cardio-metabolic challenges.
- Atypical antipsychotics which cause fatigue and sedation such as Zyprexa and Seroquel will decrease level of arousal and may cause cognitive impairment in other subscales

DLPFC Functioning circuit disruption 100% of the time
- May be indicative of ADD or ADHD
- Stimulants, wake promoters, atomoxetine and Guanfacine ER treat elevations in these scales

Cerebellar circuit disruption 100% of the time
- Dose reduction of mood stabilizers may be required after starting augmenting atypical antipsychotic by 10 to 20% over the course of months
Dosing and therapeutic drug monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li2CO3</td>
<td>300mg to 2400mg</td>
<td>0.5 to 1.5</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600-2400</td>
<td>not reported</td>
</tr>
<tr>
<td>Divalpoex/valproic acid</td>
<td>500-3000</td>
<td>50 -125 ug/mL</td>
</tr>
<tr>
<td>Lamotrigene</td>
<td>25 – 400</td>
<td>not reported</td>
</tr>
</tbody>
</table>

Correl, McIntyre et al 2010

The model offered for prioritizing medication management is one of managing limbic overactivity first. Limbic overactivity needs to be controlled with dopamine blocking medications preferentially if our prefrontal cortex is not able to do it for us. We may be able to modulate unwanted thoughts and behaviors by transiently blocking the dopamine system and then asking people to reassess their cognition with the help of a third party. It is in this way that we can precisely use the lowest possible effective dose of a medication. Knowing the frequency and severity of someone’s symptoms and their medical co-morbidities we can understand which medication might be most useful. At this time Abilify, Geodon and Latuda are the atypical antipsychotic medications which seem to have the lowest risks for causing metabolic complications and weight gain. None of the atypical antipsychotic medications can be said to be weight neutral at this time and medications that do not cause a lot of weight gain in adults can cause a lot of weight gain in children making tracking weight, blood sugars and triglycerides in this population very important. The rating scale can be divided into 7 subscale sections. The first section documents a need to treat based on the level of functioning someone has. The second is the orbito frontal pathway assessment which measures the degree to which someone may require an atypical antipsychotic medication, how much and for how long. The second page assesses symptoms of inattention or the need for a stimulant, non-stimulant or wake promoter and for how long to increase frontal lobe dopamine levels. The top of the third page assesses cerebellar symptoms by looking for side effects of mood stabilizer agents which can be lowered when atypical antipsychotics are added as augmenting agents.

The CMRS is divided up into 7 self rating subscales to complete an evaluation.

1. Function subscale documents need to treat
2. MEDIAL frontal subscale emotional control
3. Memory subscale memory formation and attention
4. Dorsal lateral prefrontal subscale attention concentration negative symptoms
5. Cerebellar subscale toxicity
6. Executive functioning subscale planning
7. Motivation subscale medical illness
The following questions regarding functioning documents a need for treatment with medication and should be verified by a third party for validity.

**FUNCTIONING**

<table>
<thead>
<tr>
<th></th>
<th>ALMOST NEVER</th>
<th>OCCASIONALLY</th>
<th>SOMETIMES</th>
<th>FREQUENTLY</th>
<th>ALMOST ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are your symptoms interfering with your work functioning?</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>2. Are your symptoms interfering with your home functioning?</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>3. Are your symptoms interfering with your relationships?</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

Functioning subscale

- Documents symptoms that are *clinically significant* and therefore need medication treatment
- Should be verified by a concerned third party
- Indicates the frequency and severity of the dysfunction
- May take a long time to improve

If someone is having challenges with symptoms causing functioning problems frequently, then they would need to assume the risk of starting a medication after a negative medical work up if it is determined that emotional challenges are causing the dysfunction. Improvement in functioning can take years with medications. The rate of brain cell receptor turn over can change over the course of weeks, months or years. It is important to clearly define the level of dysfunction at the start of any medication treatment as getting symptoms into the almost never category is the ultimate goal of treatment.

**Orbito Frontal circuit subscale**

The orbito frontal circuits document the self report of the core symptoms of anxiety, worry, racing thoughts, irritability, temper deregulation, impulsivity depression and nervousness. These symptoms correlate with many of the mood, and anxiety disorders. A serotonin dopamine antagonist or a partial agonist can be used quickly to handle these symptoms in a timely fashion and a one time test dose will tell a clinician to what degree someone's symptoms can be improved and the likely hood of the medication will provide a response. The scale is completed a second time after a one time test dose of a medication reaches peak plasma levels to determine to what degree improvement occurs. A phone call to the clinician 2 hours after a test dose is taken is very helpful in determining response as is a third party observation. If symptoms are reduced by 50% with a one time test dose then it may be that a second dose will result in complete symptom resolution. Abilify is a medication with a very long half life and if continued at a test dose level, it may cause a zombie like feeling when it reaches steady state levels in 2 to 4 weeks. Efficacy of medications is limited by tolerability. At higher doses of Abilify, people can develop nausea and
headaches after a one time test dose which subsides over the course of hours. The effect on the orbito frontal circuit subscale symptoms usually improve for 3 days as the half life of Abilify is about 90 hours making this medication very useful when a one time dose is given. A one time test dose may be life saving if consistent compliance with taking medications is a challenge for someone. An emergency situation requires the use of a medication that is predictable and has few side effects. While Zyprexa and Seroquel are often used acutely, the sedation which can accompany these medications may not be appropriate in some instances. A test dose medication should deliver a rapid response or a 50% reduction in orbito frontal symptoms. This means reducing symptoms from 100% of the time almost always to sometimes or 50% of the time. Typically, this can be done with a onetime dose of Abilify 10mg once provided the person is tolerant of the medication and has not had a history of head injury. A one time dose which permits binding of 70% to 80% of D2 receptors can result in a 50% improvement in symptoms on the rating scale which lasts about 3 days. Over this period of time, careful review of the rating scale may enable the person to understand that there is a correlation between the medication effect at two hours and a slowing of racing thoughts which can provide insight into the way the medication may work again if taken again. The challenge with taking a medication that has a very long half life at a high dose daily, is that the blood level of the medication can increase over time and a zombie like state can occur at 4 to 6 weeks. So, it is up to the clinician to decide if there is sufficient improvement after a one time dose to reduce the dose and continuously give 25% daily of the original test dose with the understanding that if a care giver or the person themselves feels the need for another one time higher dose that this can be done only after discussion with the prescriber. For people who have had severe psychosis for several weeks it may be that a dose of Abilify at 10mg a day for 3 consecutive days or longer may be necessary to saturated dopamine brain receptors for a week before a reduction is recommended. Reduced dosing of a long acting medication in this way may reduce the risk of side effects by 75% in the long term.

There is an ongoing need for monitoring lipids and blood glucose when atypical antipsychotics are used. If triglycerides do not elevate with in the first 6 weeks of taking an atypical antipsychotic, there is only a 12 % likelihood that they will elevate in the future. High doses of Zyprexa, Seroquel, and Risperdal can cause challenges with symptoms seen on the dorso lateral prefrontal circuit subscale by blocking histaminic and cholinergic receptors at high levels in this pathway leading to challenges with attention, concentration and executive functioning. If cognitive challenges do happen on one atypical antipsychotic, then a switch to another can be considered. The key to optimal functioning of orbito frontal circuits on the CMRS results from using the lowest possible effective dose necessary to control symptoms while preserving efficiency in the DLPFC. It is important to note that any medication that causes fatigue or sedation impairs arousal and affects the DLPFC thereby making this circuit inefficient. If cognitive challenges are present, it may be necessary to switch medications to one with lower side effects.

### MEDIAL FRONTALEMOTIONAL FUNCTIONING CIRCUITS

1. Have you noticed increased moodiness?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
2. Do you lose your temper more quickly than before?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
3. Do you feel depressed?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
4. Do you have feelings of anxiety or nervousness?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
5. Do family and friends comment on changes in your behavior?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
6. Do you have increased irritability?  
   - ALMOST  
   - NEVER  
   - OCCASIONALLY  
   - SOMETIMES FREQUENTLY  
   - ALWAYS
### MEDIAL FRONTALWORRY AND OBSESSING CIRCUITS

1. Are you worrying for more than 2 hours a day?  ______  ______  ______  ______  ______  ______
2. Are you having racing thoughts? ______  ______  ______  ______  ______  ______
3. Are you overreacting to situations? ______  ______  ______  ______  ______  ______
4. Do you misinterpret things that other people say to you? ______  ______  ______  ______  ______  ______
5. Do others say you are impulsive? ______  ______  ______  ______  ______  ______
6. Do you feel you are impulsive? ______  ______  ______  ______  ______  ______

### MEDIAL rontal circuits
- Documents and quantifies severity and frequency of symptoms
- More frequent symptoms generally require higher doses of an atypical antipsychotic
- Less frequent symptoms generally require lower doses of an atypical antipsychotic
- Medications with fewer side effects should generally be used first line
- People with these symptoms may generally have mood disorders, anxiety disorders and psychotic disorders
- Atypical antipsychotics may be used as initial treatment or 2 weeks after starting an antidepressant
- A one time test dose should be dosed to get a 50% improvement in symptoms after 2 hours.

### Meso Cortical memory circuit pathway subscale
The meso cortical circuit subscale is used to document memory challenges someone may be having. Alzheimer’s disease memory loss is usually never reported by a person with Alzheimer’s. Family members are usually the ones to report their concerns to the physician about a demented relative. It is possible that if someone does not have neurologic or metabolic problems and is experiencing memory problems confirmed by another person, they may be depressed. Alcohol and drug misuse of the benzodiazepine class as well as sleep deprivation can cause dysfunction in this pathway as well and are important considerations for the clinician. If done correctly, medication treatment of inefficiencies of other pathways should lead to improvement in memory unless the person has Alzheimer’s disease. Improvement in memory functioning may occur with lifestyle changes unless a chronic severe progressive neurologic condition occurs. Schizophrenia does not result in memory decline as time goes on above that seen in normal aging. Schizophrenia causes problems with memory formation and not retention. Similarly some people with mood swings can have challenges with memory formation as a result of fluctuating mood states. When their mood states are regulated the memory concerns improve.
Meso cortical circuits

- If someone is complaining of memory problems they are most likely depressed
- If someone is complaining about a spouse’s memory problem, the spouse may have Alzheimer’s disease
- If the orbito frontal circuits are inefficient they may be causing memory challenges as memory is dependent on one’s emotional state
- If the DLPFC or cerebellar circuits are inefficient they may be causing memory challenges as good memory is a product of excellent attention

Dorsal Lateral Prefrontal concentration circuit subscale

The Dorsal lateral subscale or DLPFC is a very hyper-metabolic area of the brain which uses glucose and oxygen seen on FMRI scanning proportionally to the amount of energy expended in mental energy or work. On FMRI scanning, a series of mental gymnastics like the Wisconsin card sort or N – back test will cause the DLPFC to work harder and can cause a 2 to 3 % reduction in the amount of oxygenated to deoxygenated hemoglobin in the blood which is detected by the new scanners that are now available. While many of us cannot readily access and utilize these scanners at this time as a diagnostic tool, as technology improves, the cost of scanning will decrease over time as the rate of progress of computational work increases. If someone has a low dopamine tone in the DLPFC as a result of a factor such as the VAL VAL genetic polymorphism for the COMT gene, it may be that a dopamine agonist, l-methyl folate or a dopamine partial agonist may be helpful to improve the symptoms on this subscale. Other agonists may be used as well such as Wellbutrin, Strattera or MAOIs, but there is a risk of destabilizing moods by way of phasic firing of the orbito frontal pathways. In general, it is safe to treat and stabilize the orbito frontal pathways first before improving the efficiency of DLPFC using a serotonin dopamine antagonist (SDA) or dopamine partial agonist (DPA). There are many ways of improving the DLPFC efficiency which includes Guanfacine ER an alpha 2 agonist Intuniv (Guanfacine ER) can increase growth hormone release and help recovery sleep by causing sedation while increasing dopamine levels in the DLPFC to improve attention concentration and focus. Wake promoters do an excellent job increasing dopamine in the DLPFC. Medications like Provigil (modafanil) or Nuvigil (armodafanil) increase histamine release in the nerve cells in the lateral hypothalamus and can reduce fatigue. For people who suffer from chronic neurologic illness such as multiple sclerosis and sleep apnea, shift work disorder or narcolepsy, wake promoters can be very helpful medications. It is important to note that any medication that causes fatigue or sedation impairs arousal and affects the DLPFC making this circuit inefficient. Isolated DLPFC circuit functioning can be improved off label with stimulants and non-stimulants (Strattera, or Guanfacine ER). The risk of mood cycling using stimulant medications is lower than the risk of cycling on antidepressants. The risk of cycling may be increased using Strattera (atomoxetine) which is a selective norepinephrine antagonist that also increases dopamine in the frontal lobes. It is preferable to use long acting preparations of a stimulant medication to prevent rapid fluctuations in blood levels and the longest acting amphetamine preparation which has the least potential for abuse is Vyvanse. Vyvanse is Lis-dexamphetamine and is a pro-drug. It becomes active only after its lysine group is cleaved off by enzymes making this preparation unlikely to be abused by injection or snorting. Vyvanse has a half life upward of 14 hours.
Paradigm for mood stability

| 1. | Stabilize orbito frontal pathway first |
| 2. | Stabilize DLPFC second |
| 3. | Improve cerebellar functioning last. |

“We put out the sub cortical Limbic fire First Before dealing with Cortical fire Second”

<table>
<thead>
<tr>
<th>DLPFC ATTENTION AND CONCENTRATION CIRCUITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you having difficulty concentrating?</td>
</tr>
<tr>
<td>2. Do you have difficulty concentrating in noisy environments?</td>
</tr>
<tr>
<td>3. Do you have difficulty concentrating on more than one thing at a time?</td>
</tr>
<tr>
<td>4. Are you having difficulty focusing your attention while reading or watching T.V.?</td>
</tr>
<tr>
<td>5. Are you having difficulty staying focused as a passenger in a car?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DLPFC LANGUAGE AND COMMUNICATION CIRCUITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have difficulty understanding others?</td>
</tr>
<tr>
<td>2. Do you have problems expressing yourself in writing?</td>
</tr>
<tr>
<td>3. Are you having difficulty expressing yourself to others?</td>
</tr>
<tr>
<td>4. Do you have difficulty spelling words?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DLPFC ORGANIZATION AND SEQUENCING CIRCUITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have difficulty following driving directions?</td>
</tr>
<tr>
<td>2. Are you having difficulty opening your mail on a regular basis?</td>
</tr>
<tr>
<td>3. Are you having difficulty doing or keeping up with household chores?</td>
</tr>
<tr>
<td>4. Are you having difficulty doing more than one thing at a time?</td>
</tr>
<tr>
<td>5. Are you having difficulty effectively managing your time?</td>
</tr>
</tbody>
</table>

DLPFC (Dorso lateral pre frontal cortex) circuits

- Once the orbito frontal circuits are made efficient then stimulants, non-stimulants or wake promoters can improve DLPFC circuits.
- Medications that improve the DLPFC circuits include Amphetamines and methylphenidate treat ADHD
- Wake promoters like Nuvigil or Provigil treats sleep apnea
Cerebellar balance coordination sensory circuits

These circuits can give an indication as to whether someone may be having side effects on anti-seizure agents or mood stabilizer medications that effect ion channels directly. The atypical antipsychotics can be used in augmentation therapy with mood stabilizers to reduce mood stabilizers to the lowest possible effective dose to reduce the long term risk and burden of these medications. It may take a few weeks of augmentation with an atypical antipsychotic for a dose reduction in mood stabilizers to occur as a result of fatigue. The cerebellum is responsible for much of our smooth motor coordination but it is also able to play a role in the rate and coordination of our thoughts. Many medications and drugs affect cerebellar circuits such as alcohol and a pattern of alcohol use may be suspected if these coordination circuits are associated with memory circuit dysfunction. These circuits may also be disrupted in neurologic disease such as multiple sclerosis. Chronic pain people who use excessive amounts of narcotics can have inefficiency of their cerebellar circuits and these circuits may be adjusted by the use of antidepressants, anti-seizure agents or alpha 2 delta ligands such as pregabalin or gabapentin. Lamictal has helped many people who have had challenges with reflex sympathetic dystrophy and fibromyalgia. Fibromyalgia as a pain syndrome is helped by exercise which helps pain by causing de-sensitization. The tricyclic antidepressants have been used in chronic pain at lower doses (10mg) and can reduce the need for analgesics at high doses. The atypical antipsychotic Seroquel XR has been able to treat pain, depression anxiety and bipolar depression (on label) through an NRI or a norepinephrine reuptake mechanism of action at 300mg bedtime or higher.

There are some clinicians who believe that a possible biomarker for Alzheimer’s disease may be a loss of smell but it is difficult to distinguish loss of smell due to a progressive neurologic illness or a loss of smell secondary to smoke or another environmental etiology. Cerebellar symptoms can occur when mood stabilizers are given at very high doses and these doses can be reduced using the atypical antipsychotics such as Abilify and Geodon as augmentation strategies. Benzodiazepines can cause coordination problems seen in people who are using or have used alcohol in the past to excess. A low dose of a dopamine partial agonist off label may be able to facilitate a dose reduction of a benzodiazepine with a one time dose as the anti anxiety effect caused by both is 5HT1A partial agonist effect and 5HT2A antagonism effect. Benzodiazepines may also be able to have their dose reduced by the use of Neurontin and Lyrica off label. Lithium Tegretol and Valproate doses may be able to be reduced if they are causing cognitive, memory and cerebellar problems using Abilify or Geodon as an augmentation strategy on label. Dizziness needs to be specifically determined to be either lightheadedness or vertigo which manifests as a symptom of the room spinning. Problems with sensory gating may be indicative of sensory pathway neurodevelopment problems. This may suggest a more chronic problem with synapse formation challenges, apoptosis and nerve cell migration. Sensitivity to light may be the result of taking medications which have energy absorbing cyclic ring or double bond structures which can absorb high energy sunlight causing sunburn requiring the need for pre-exposure sunscreen. Visual changes that cause objects to seem closer or farther away than they actually are may be secondary to an underlying neurological challenge such as a seizure disorder. Double vision or blurred vision may be side effects of mood stabilizers taken at high doses. Being nauseated is not typically thought of as a cerebellar pathway symptom but can be a side effect of an Abilify 10mg test dose. Persistent post concussive syndrome symptoms are manifest by headaches, sensitivity to light and sounds, memory deficits dizziness and reduced inhibition. Polypharmacy
can make it unclear if a symptom is a side effect from medication or a symptom of an illness. The only way to determine if a symptom is a side effect is to reduce the medication that is at the highest relative effective dose compared to another medication. Have its dose reduced once and see if the side effect resolves.

<table>
<thead>
<tr>
<th>CEREBELLAR BALANCE/COORDINATION/SENSORY CIRCUITS</th>
<th>ALMOST NEVER</th>
<th>OCCASIONALLY</th>
<th>SOMETIMES</th>
<th>FREQUENTLY</th>
<th>ALMOST ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you find you have difficulty with handwriting, hitting a ball, riding a bicycle or doing something that used to be easy to do?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have problems with balance or coordination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you experience dizziness?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you experience loss or decrease in sense of taste?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you experience loss or decrease in sense of smell?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you experience physical pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CEREBELLAR VISUAL-PERCEPTUAL CIRCUITS</th>
<th>ALMOST NEVER</th>
<th>OCCASIONALLY</th>
<th>SOMETIMES</th>
<th>FREQUENTLY</th>
<th>ALMOST ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have increased sensitivity to light?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do objects seem closer or farther away than they actually are?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. When reading do printed letters appear to change or change position?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you see two of things when there is only one?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you have difficulty focusing your eyes on objects?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you feel nauseous?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cerebellar circuits**
- May indicate toxicity from mood stabilizers or an underlying neurologic illness
- A one time dose reduction may be warranted if these symptoms are judged to be caused by a medication.
- A ten percent reduction in a dose of a medication once may be indicated for side effects occurring occasionally
- A twenty percent dose reduction once may be necessary for side effects occurring occasionally
- A fifty percent dose reduction once may be necessary for side effects that are occurring sometimes or 50% of the time.
- Repeating the self rating scale determines if an improvement has occurred and if a sustained reduction should occur over the next month

**Executive functioning circuit scale**
Once the previously mentioned rating sub-scale symptoms are in the almost never category then planning for the future can occur. Dopamine drives the prefrontal cortex executive functioning subscale and fine tuning may be needed but psychotherapy exercise can help motivate many people and drive them to succeed. Executive functioning subscale is mediated primarily by the dorsal lateral prefrontal cortex which integrates the processing, interactions, and output of other cognitive processes such as language and memory carried out elsewhere in the brain. Although the dorso lateral prefrontal cortex is essential for executive functioning, there is evidence that the anterior cingulate and the lateral orbito frontal sub cortical circuits are also involved in the development of executive functioning. Dysfunction of these circuits can result from disruptions of multiple neurotransmitter systems including glutamate, acetylcholine, dopamine, norepinephrine, serotonin and GABA. Executive dysfunction can occur as a result of direct injury to these circuits which can be cortical, sub cortical or axonal. The best way to improve executive function is to optimize physical health and then address as many non-invasive ways as possible to increase dopamine in the frontal lobes. Using omega 3 fatty acids may help improve myelination of axonal fibers and improve processing speed and efficiency. It is important to understand that executive functioning like many other aspects of cognition is influenced to a large degree by sleep, energy anxiety racing thoughts and irritability. Executive functioning or planning is influenced by our ability to see a vision of potential in our mind. This vision of what we can accomplish affects our planning ability. Past experience helps us see the possibilities that lay ahead. If we have lived in an impoverished existence longstanding, then our ability to visual a different future is difficult. If we can see a potential life for ourselves that is rich and fulfilling we may be able to better plan to forward ourselves. The motivation to plan is a product of energy, passion and purpose and is modulated by neuronal firing in the dopamine system. A low dose of Abilify may be able to improve executive dysfunction by acting as an agonist in the frontal lobes and by providing a low grade sense of restless energy which tends to be motivating. This restless energy at a low dose is not typically identified as being uncomfortable as high doses that cause akathisia are. The good news about using a low dose of Abilify is that people tend not to sit around when they feel slightly restless. Nature has made it possible for us to feel a certain amount of anxiety first before having the motivation to change our environment occurs. Care in dosing of Abilify has to be taken in all individuals so that the dose is high enough to promote an effect of symptom relief. The dose should not be high enough to cause akathisia which can occur in doses of Abilify above 5mg daily in middle aged individuals.
• Planning and purpose manifests from overall cognitive improvement and is the result of treatment

The motivation and fatigue subscale circuits
This scale will tell a prescriber the validity of the previous responses on the prior subscales. Exercise usually brings on fatigue in most individuals and motivation is usually lower when fatigued unless you happen to be a world class athlete. This subscale is also a screen for identifying potential underlying medical problems may have such as sleep apnea, head injury, and peri-menopausal symptoms which can complicate a presentation of symptoms. Dreaming allows prescribers to understand if someone has been sleeping well and may promote a discussion about sleep.

<table>
<thead>
<tr>
<th>MOTIVATION/FATIGUE/TIREDNESS</th>
<th>ALMOST NEVER</th>
<th>OCCASIONALLY</th>
<th>SOMETIMES FREQUENTLY</th>
<th>ALMOST ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does exercise bring on fatigue?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is your motivation lower when you are fatigued?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Are you trembling or shaking?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Are you having hot flushes or chills?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Have you ever had a head injury?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Have you had any recent surgeries?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have any medical problems?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you dream at night?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you snore?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The motivation and fatigue subscale:
• Assesses the hypothalamic-pituitary-adrenal axis (HPAA)
• Head injury may guide the need for a reduction in atypical antipsychotic dose
• Sleep apnea may guide the need for dose reduction
• Co-morbid medical problem screen

Sleep and recovery
We all need to get the type of deep restful recovery sleep that young children seem to be blessed with. The type of sleep that prevents children from being awakened despite hitting their head on a car door frame as you pick them up out of the car after a long drive. As they sleep in this almost coma like state, they are releasing growth hormone to help their muscles recover from running around outside all day, they release more melatonin at night because of this daylight activity and their daytime cortisol levels reduce. Recovery sleep lowers cortisol levels put less stress on the hippocampus allowing it to do its job of transforming stem cells into new nerve cells. In this relaxed state the hippocampus, our memory center, forms new synapses and stem cells differentiate into new neurons. All this happens while we are dreaming. As we go safely insane every night while we sleep, we do things in our dreams that we would never do in our real life and we can’t even reliably assess how long we are doing them for. This occurs because our frontal lobes are responsible for both our judgment and time perception and when we sleep, our frontal lobes disconnect from our underlying limbic structures making our limbic system responsible for our night time reality. Without frontal lobe inhibition, our underlying limbic system is free to ride without any structure unleashing our primitive urges. Unbridled from our cortex, our judgment in
our dreams is terrible and our time perception is even worse. Our frontal lobes are responsible for
our ability to judge time and monitor the appropriateness of our behaviors. It is interesting that
some people are blessed with the ability to solve problems in their sleep. These people
apparently do not have a total disconnect of their frontal lobes from their limbic system during
sleep as the majority of people do. They can direct their mind to work while they sleep. By asking
themselves questions before they go to bed, they can apparently tap into a lasting connection
between the frontal lobes and the underlying limbic ring of organs that creates our reality while we
sleep. These people may truly be able to work 24/7 in their minds and can be exceptionally
productive and brilliant even during the next day. The rest of us are left to recover and sleep one
third of our lives away. Fortunately, for many people, sleep medications are some of the most
effective treatments we have in medicine. If physicians can do something very well is that we can
put people to sleep with medications. When sleep medications do not work, however, we need to
look at underlying metabolic causes such as sleep apnea and thyroid disease. Sometimes racing
thoughts and extreme anxiety can be complicating variables and override the effects of sleeping
agents. Sometimes additives, alcohol and drugs will influence our much needed perfect sleep.
Sometimes, sleeping agents can cause memory loss and it is most wise if people who take these
medications do not speak to anyone after taking these medications as things can be said, events
can happen under the influence of these medications and not be remembered which can cause
much embarrassment or worse. Sleep deprivation is becoming more problematic as many
Americans drink coffee by the gallons every year and although the rest of the world recognizes
that we are the most productive nation in the world, it comes with the expense of insomnia or the
inability to sleep at times. One large Grande drip Starbucks coffee can have an astounding 520mg
of caffeine and can cause a noticeable hand tremor as well as irritability. The power of coffee is all
consuming to many who permit their restful recovery sleep to suffer at the expense of improved
attention and wakefulness during the day. There are medications available now that promote
wakefulness and highly focused attention and concentration without the irritability and hand
tremor that the wakeful bean can cause. Most Americans now sleep 6 hours a night during the
week and play catch up on weekends. How much of this is a result of excessive caffeine intake is
not certain.

Adolescents with sleeping problems have attention, concentration and mood problems that can
lead to poor school performance not to mention car accidents. One late night of partying in an
adolescent can cause cognitive impairment that can last for days in susceptible individuals.
Insurance companies have known for years that a brain does not fully develop until the age of 25
when myelination is completed which is when car insurance rates drop. A sure sign of sleep
deprivation is seen in some people who have to fall asleep quickly during the day and
instantaneously start dreaming. The ability to nod off quickly and dream during the day is not a
blessing. Napping spontaneously during the day is a sign of sleep deprivation and probably sleep
apnea if someone has a neck size greater than 18 inches associated with snoring. The best way
to cure sleep deprivation is to stick to an early bedtime, limit any TV watching, keep the bedroom
room temperature at 65 degrees, sleep with blankets and not turn on bathroom lights when having
to go to the bathroom at night. Many people who do not have regular routine sleep patterns find
that over the counter medications and alcohol sort of work. Medications like Xanax are frequently
prescribed which work quickly and predictably in 20 minutes to change a mood dramatically and
promote sleep. Medications like Xanax are often taken in crisis situations and help people
immensely. For students however, the memory loss that occurs with benzodiazepine use while
studying can be disappointing. Omega 3 fatty acids can help young minds sleep better and may
aid in myelination. Adolescents can reduce cortisol production during the day and elevate

Page 20
The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
melatonin production at night simply by exercising in bright sunlight daily. Doing this alone may preclude the need for taking a sleeping agent designed to shut down the frontal lobes which enables the sub cortical structures to separate and recover on their own at night. Adolescents do well taking fish oil supplements at night to help with sleep provided they are unable to take in a diet rich in colorful veggies and get fish oil from wild Alaskan salmon. Omega 3 fatty acids have few side effects if molecularly distilled preparations are used, may promote brain myelination, reduce inflammation and fish oil has been shown to delay the onset of psychotic symptoms in prodromal high risk children. It is always important to understand that living like one's ancestors lived and rejoicing in exercise during the day in sunlight will usually provide restful sleep and allow a brain to grow and develop naturally.

Elders deserve and require the recovery sleep younger people get. Elders who take benzodiazepines or histaminic or cholinergic medications may have balance problems and represent a fall risk. Sleeping pills and alcohol should never be taken together as many unfortunate deaths happen this way every year. Often what we do as physicians is take away things 90% of the time to improve people’s lives. An example of this is the cognitive improvement we often see when we stop people from taking over the counter sleep aids. Changes in cognition can occur when people have problems sleeping and happen when over the counter medications are used to promote sleep as any medication or drug that causes fatigue will cause cognitive impairment. The CMRS may be able to detect subtle changes in cognitive functioning as a result of medications used to help people sleep. Older people who worry or suffer from anxiety either physically based in the form of panic or centrally based (in the brain) in the form of ruminating about the same topic over and over again, do well with serotonin based antidepressants like Celexa or Lexapro unless they have a cycling mood disorder. These highly selective agents put a wet blanket on the dopamine system and produce a sense of relaxation. Most of the serotonin receptors we have in our bodies are located in our gut and it is important to monitor weight for any one taking psychotropic medication. The SSRIs or SNRIs can help people who are anxious sleep well at night. Insomnia can be easily treated with a sleeping medication. Although older people who take Xanax rarely run into challenges unless they are using alcohol with it or have a past bad history of alcohol misuse, there are other medications we have at our disposal which can improve sleep without incurring much risk of side effects. The memory subscale circuit score may be adversely affected by sleep aids which work through histaminic and nicotinic mechanisms of action as well as by drugs of abuse. Providers as well as caregivers need to be aware of this possibility and monitor the use of these medications. Any medication that is used for sleep needs to be used at the lowest possible effective dose as any medication that causes fatigue is likely to cause memory problems at a high enough dose or possibly even at a low dose in susceptible persons especially for those people who are at the extremes of age. For people who have had challenges taking antidepressants, sleeping medications or anti anxiety medications like Xanax, an alternative option is the use of the atypical antipsychotics for sleep off label. The atypical antipsychotic medications were initially studied in severely disturbed schizophrenic people and are now found to be safe and effective for treating certain symptoms in people who do not have as severe an illness as schizophrenia though they also carry a risk of weight gain. The elderly can benefit from using atypical antipsychotics medications sparingly for a time limited period at lower doses to treat irritability and anger. The elder’s body is also susceptible to cardiovascular events especially if they have dementia and use these medications. The elderly who suffer from dementia with psychosis appear to be at increased risk of death using these medications for unclear reasons. The point is that these atypical antipsychotic medications are powerfully effective
medications when used appropriately and sparingly. The atypical antipsychotic medications are to be used sparingly and very carefully in the elderly. Monitoring with a rating scale such as the CMRS may be helpful as a guide to being able to use the lowest possible effective doses of these medications for the shortest duration possible to avoid side effects until behavioral remedies can be implemented so that the drug can be withdrawn. It is important to know that just because a medication works for specific symptoms of aggression in the elderly in the short term, this does not mean that the continued improvement is completely due to the medication and it may be worthwhile to stop the medication after 6 months to see if the behavioral problem has resolved on its own. The brain, even in older people, retains an ability to form new neurons and can adapt as it was initially designed to do if it is treated appropriately. The brain has an easier time of adapting if it is well taken care of and not subject to toxin exposure and gets needed rest. There are many behavioral methods that can be used to help keep an aggressive elders behavior under good control. When a strong elderly person is aggressive, a rapid acting atypical antipsychotic can be very helpful in enabling the person to control their behavior. Unfortunately, the atypical antipsychotics which help with sleep the most, Zyprexa and Seroquel may also cause weight gain through a serotonin, histamine and muscarinic end organ mechanism of action. Yet, very low doses of these medications can help people sleep, can control irritability and may be used sparingly off label until behavioral methods start working. The CMRS scale can enable a prescriber to reduce the dose needed of an atypical antipsychotic to get to the lowest possible effective dose and if the medication is needed indefinitely, the scale can help guide a switch to another medication which has fewer side effects. It may take a lot of front end effort initially filling out a rating scale to document need for treatment and symptoms but the effort is worth it in the long run. Behavioral techniques like progressive muscle relaxation, mindfulness training and self hypnosis are well known and effective ways to help people to sleep. I often refer people to a local Barnes and Noble bookstore to get more information on behavioral methods to help them get to sleep. It is important to understand that the newer atypical antipsychotics are not as sedating as the older agents. The newer agents can be used to help people sleep none the less if they are having multiple symptoms on the rating scale that are preventing them from sleeping and if they are dosed high enough. Like adolescents, elders require an excellent diet and daylight exercise to promote good recovery sleep.

Energy and the 5 Dopamine pathways of pain and pleasure
Dopamine is the pleasure chemical in our brain. The important decisions we make are usually based on either maximizing the pleasure we derive from what we do or avoiding pain. Understanding the 5 dopamine pathways and the principles of pain and pleasure is crucial to understanding thinking and behavior. There are 4 dopamine pathways which are modulated by medications which can work as agonists, antagonists and partial agonists to help improve our energy. The first is the pathway from our brainstem to the frontal lobes called the meso cortical pathway responsible for determining our level of alertness. The second is the meso limbic pathway which is responsible for our ability to experience pleasure and reward. The third is the tuberoinfundibular pathway which regulates our hormonal system and the fourth is the nigrostriatal pathway which controls our motor system. The fifth thalamic pathway we know little about. Each of these pathways is affected by medications that work through a dopamine mechanism of action and can control various aspects of our cognition as well as movement. The challenge is to develop an understanding of which of these pathways are inefficient and make them more efficient using many different therapies. The CMRS has been designed to look at orbito frontal circuits first as many emotional functioning and worrying/obsessing symptoms occur secondary to inefficiency of these pathways. Orbito frontal pathway circuit inefficiency needs to
be addressed first in order to improve functioning at home work school and relationships. If these subscale scores are not dialed in precisely first, then it is difficult to improve cognition secondarily. Passion and motivation come from dopamine releasing neurons located in our brainstem. The energy we have is a product of our dopamine system firing at an increased tonic rate throughout the dopamine system. There is a spectrum by which this firing can happen. This firing occurs on a continuum in various areas of our brain determines our thoughts and behaviors. For example, it is the spectrum of firing in our frontal lobes that determines modulation of our attention, focus and concentration. A very low level of firing causes a lack of interest in activities and apathy, a cognitive symptom, results. A high a level of firing can cause anxiety and psychosis. A performance and anxiety curve is a bell shaped curve meaning at low levels of arousal a low level of performance occurs and a low level of performance occurs with an excessively high level of arousal. The best performances occur when there is a moderate level of arousal.

Parkinson's disease is an illness which results from a loss of dopamine neurons in the substantia nigra in the brain stem. Many of these people start to develop a low energy mood state before symptoms of the movement disorder begin. In Parkinson's disease mood symptoms do not necessarily correlate with severity of the motor symptoms. Low levels of dopamine in the brain in various areas can have profound effects on motor development and mood. Exercise and deep breathing changes our physiology and mood state by increasing dopamine output in an instant, provided we are hard wired to be able to move about and provided the neurons in our brainstem are functioning well. Those of us who have inefficiency of our neuronal circuitry need to explore ways to improve these circuits and the CMRS, if done every morning, can help guide a provider to tell us if what we are doing therapeutically in the form of exercise, eating, and supplements are helping us or not.

Dopamine pathways are complex and seem to be responsible for our ability to have both passion and purpose. It is easy to see why there is a high incidence of low energy mood states in people with Parkinson's disease and addictions. In fact, low energy mood states are seen in many neurologic illnesses such as post stroke illness, Alzheimer's disease, Huntington's disease, traumatic brain injury, multiple sclerosis and epilepsy.

Problems regulating our dopamine pathways involve many challenges that people have with many different medical illnesses. So, how do we choose from among all the drugs that work through a dopamine mechanism of action to help someone develop energy? This is a difficult question to answer. The decision of which drug to use to treat orbito frontal symptoms depends on the severity and frequency of the symptoms and the availability of someone else to help observe the person and help them monitor symptoms and treatment. We know that many serotonin dopamine antagonists and partial agonists have side effects so it makes sense to use the medications that have the least amount of risk of causing weight gain and side effects first unless an emergency situation dictates otherwise.

Medications that improve isolated DLPFC functioning include the stimulants, Strattera, Provigil, Nuvigil, and Intuniv Guanfacine ER. Medications that are labeled as antidepressants that have an effect on mood symptoms and circuits in the orbito frontal cortex include Wellbutrin and Zoloft (high dose). Many of the newer medications give energy and treat mood symptoms at a low dose. These multifunctional drugs produce sedation and control psychosis at higher doses. These multifunctional drugs include Abilify and Geodon Saphris and Latuda.
Anxiety and pain

Pain is mediated by 3 different major nerve fibers in the brain. They are called the alpha beta fibers, the alpha delta fibers and the c fibers. The alpha beta fibers respond to a soft touch. The alpha delta fibers tell us that we have sustained a significant tissue injury. The swelling of tissue from inflammation, the release of histamine to fight an infection that may or may not be present in the body is perceived as painful by the alpha delta fibers. The c fibers carry afferents to the thalamus telling us that there is nerve damage or pain and this pain can be excruciating for some. Pain alerts our attention rapidly and effectively through phasic firing of nerve cells. This firing can be unrelenting unless it is modulated. People with chronic pain may or may not have identifiable tissue damage. An example of this is a condition called fibromyalgia where people who do not have tissue damage suffer from tender points along their muscles and joints. Many psychiatrists see these people as suffering from a depression. There are many others who have this illness who do not have a detectable emotional disorder. They simply have pain. Pain therefore manifests in our brain and we can perceive it or not perceive it in our pre frontal cortex. How this occurs is a manifestation of the way our neural circuits are hard wired. Professional athletes are paid to play their sports despite having sometimes severe physical injury. How this is done is a manifestation of hormonal release of endorphins and a decision by a frontal lobe to continue despite severe pain signals coming from the body. The problem with pain is that these signals can get confused when medications to treat pain are used in a non-rational manner. Pain medications should be given to treat a condition that identifies the etiology of the pain to the best extent that one understands. The antidepressants Savella, Pristiq, Effexor XR and Cymbalta are serotonin norepinephrine reuptake inhibitors and improve pain by increasing descending norepinephrine tone down into the spinal cord blocking ascending pain fiber signal transmission. The probably also will work for vasomotor symptoms at higher doses. The response people have to these medications is on par with how the antidepressants work to treat low energy state, namely 1/3 get a response meaning they get 50% better, 1/3 get into remission meaning they get completely well and 1/3 have no response and may go on to being called treatment resistant if they have 2 antidepressant trials in a single episode of a low mood state at therapeutic levels for an adequate duration of time. If people do not respond to an antidepressant they may have a medication like Neurontin (gabapentin) or Lyrica or (pregabalin) used to effect voltage sensitivity calcium channels. These medications modulate pain pathways and can be used in the treatment of disorders like seizures, diabetic peripheral neuropathy and post herpetic neuralgia. These drugs bind to the alpha 2 delta subunit at voltage sensitive calcium channels and are tolerated very well. They are small molecules and structurally resemble the major inhibitory amino acid in the brain GABA. They look structurally similar to the amino acid leucine. The Alpha 2 delta ligand drugs have fewer side effects in general than the benzodiazepines. Often they can be used off label to treat anxiety and work very well in people who have had used benzodiazepines in the past and can be used in people who have had untoward reactions to them or alcohol. The dose that elders can use is Neurontin 100mg three times daily. Young people can use 300mg three times daily and some people with seizure disorders are prescribed much higher doses.

Chronic pain may also be treated by Lamictal off label which works through voltage sensitive sodium channels and inhibits the release of glutamate. Lamictal is used to treat people with seizures and is also approved for the maintenance of Bipolar 1 disorder. Lamictal is usually titrated slowly upwards and dosed at 300mg for chronic pain and 200mg for people with mood swings and much higher for seizure disorders. Anxiety can be looked at as a serotonin based phenomena and can be divided into 2 separate categories. The first is a physical anxiety state which is described as panic and the DSM 4 criteria lists 15 symptoms of panic. Panic may
represent a medical emergency and should be treated as such. The physical anxiety that someone can get from being anxious can lead to suicidal thinking. Worry is the thinking over and over again about the same topic and needs to be distinguished from racing thoughts which are primarily dopamine mediated. While racing thoughts get better with a dopamine antagonist, and worry gets better with a dopamine antagonist, racing thoughts tend to get worse with taking a serotonin selective reuptake inhibitor, serotonin norepinephrine reuptake inhibitor and other antidepressants. Medications that help with anxiety ssris, serotonin norepinephrine reuptake inhibitors, alpha 2 delta agonists, Lamictal for bipolar type 1 maintenance, Almost all of the atypical antipsychotic medications will treat anxiety though a powerful serotonin 5HT2A antagonism mechanism of action. Pain gets our attention like nothing else. Opiates help with severe bone pain or the pain of fractures. Opiates can cause problems with reduced testosterone levels. Valium is used in chronic pain syndromes; but it can cause memory challenges, muscle relaxation and weakness. It is important to understand that pain and arousal circuits can be modulated by several methods around a set point as seen by using treatments like deep brain stimulation and possibly transcranial magnetic stimulation. Modulating these pathways can be accomplished by using multifunctional drugs or drugs that work at different receptor sites at varying doses.

Racing thoughts and irritability
Identifying racing thoughts someone may be having can be a challenge. People with racing thoughts are not aware that their thoughts are racing about 50% of the time making information from a third party very important to have. Racing thoughts may point to someone having a cycling mood illness and may in fact be the most important symptom adults and children may present with to guide a prescriber to correct treatment. Explaining to someone that racing thoughts are thoughts that jump from topic to topic is usually clearly understood. Many people worry or think about the same topic over and over again in addition to having racing thoughts. Racing thoughts may represent a medical emergency when severe enough. They are rarely viewed as such by the person having them however. The orbito frontal pathways will usually show deregulation of many dopamine pathways if racing thoughts are present to a clinically significant degree as seen on the CMRS. Medications we have to modulate the dopamine pathways include Abilify, Geodon, Seroquel, Risperdal, Latuda, Saphris, Zyprexa and Lithium.

Pediatric bipolar disorder is a controversial issue and studies have been famously inconsistent. While we await final pediatric bipolar disorder criteria approval in DSM 5, we have many children and families who are in need in the United States. There has been a 40 fold increase in the number of bipolar children diagnosed in the US over the last decade. The broadening of the criteria has led much of this increase but aggressive disruptive behavior is a major cause as well and clinicians may have been placed in situations frequently where they have had to give a diagnosis to a child in order to medicate someone acutely. Many studies have shown that children with mood instability do not go on to develop bipolar disorder but there are studies showing that early onset mood instability does lead to an increased risk in the future. Disruptive symptoms may require short term treatment with medications which are discontinued after a family enters therapy. The normal development of a child’s brain requires it to grow in an outdoor environment facing survival while in a state of near constant movement and these are circumstances that the average child sitting in front of a TV simply is simply not exposed to. If we re-create this outdoor learning environment daily for our children and have them adopt a diet that our ancestors ate, brain development would be optimized and aggressive and disruptive behaviors may not be seen. Regardless, the aim is to treat symptoms as precisely as possible

Page 25
The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
with the goal of getting dysfunctional kids back functioning in school as quickly as possible by using medications at the lowest possible effective dose. Children with more chronic challenges may need to remain on medications indefinitely unless optimization of diet and lifestyle can occur. It is best to start off with a medication that has the lowest risk of causing metabolic syndrome at the onset and a one time test dose of Abilify can provide information as to how tolerable the medication is. A one time test dose also provides an opportunity for someone to self observe a benefit of medication as they fill out a rating scale daily so they can see for themselves if the medication is helpful or not. Multiple subscale challenges are caused by multiple factors in young children. The differential diagnosis in this population is complicated and challenging as their minds are always adapting to the environment and as a result they may present differently with vastly different symptoms at each meeting with a health care provider. In adults, the brain has fully myelinated and developed by age 22 and a diagnosis of anxiety or mood cycling problems usually does not change much. The diagnosis of bipolar disorder is very important to make in children as a delay in appropriate diagnosis and treatment can lead to multiple psychosocial challenges which may be avoided. Children need to be able to stay in school to learn to be afforded every opportunity to learn there. There are two general schools of thought with respect to being able to make a diagnosis of bipolar disorder. The major issue is if euphoria and grandiosity is necessary to have a diagnosis of bipolar disorder or if irritability and rage are necessary to have to make the diagnosis. I believe that both of these symptoms occur as a result of racing thoughts or the subjective experience that thoughts jump from topic to topic. The result of racing thoughts and whether it ultimately manifests as euphoria and or irritability is a product of how the child was raised to perceive the world. A kid raised on the west coast in an environment where everything seems to work out for the best is going to have a different perspective on life when compared to a kid raised on the east coast where survival is perceived as a fight. It may be that both of these seemingly divergent symptoms are a manifestation of how the child views the world and how they were taught to view the world. A child raised in an environment where anything is possible may breed true for classic euphoric mania. The reality of a disenfranchised existence may lead to a sense of frustration and anger and manifest as irritability. The point is that the thought process behind these two seemingly divergent sets of symptoms are the same, namely, they both are driven by a thought process that jumps from topic to topic. When a person’s thoughts race or jumps from topic to topic, it appears as if the usually logical dominant hemisphere shuts down and the non-dominant side that pulls pieces together and jumps to conclusions takes over. Racing thoughts cause someone to make connections that are not apparent to others. Racing thoughts can seem perfectly rational to the person experiencing them. While racing thoughts promote out of the box thinking they often lead to impulsive decision making which usually improves with a 10 to 20% slowing of thought process on an atypical antipsychotic. The CMRS can demonstrate the extent to which someone’s thoughts are racing. In a high energy manic state, self reflection is wrong 50% of the time. It is interesting that in a high energy manic state, getting adequate sleep is not perceived as a priority and the general perception of racing thoughts being pleasurable may lead to non compliance with medication treatment.

What theoretically causes racing thoughts?
Theoretically, tonic firing of meso limbic neurons from the brainstem determines the stability of our mood, thought process, and behaviors. It is thought that racing thoughts are a manifestation of phasic firing of high energy dopamine releasing neurons in this specific pathway. This pathway is devoid of 5HT2A receptors so that the atypical antipsychotic can work to shut down the firing in this pathway rapidly and reliably by slowing racing thoughts in both children and adults while at the same time increasing release of dopamine in the nigrostriatal and tuberoinfundibular pathways.
to reduce the risk of extra pyramidal side effects, tardive dyskinesia and prolactinemia. The core symptom of racing thoughts where thoughts are perceived to jump from topic to topic, is what is important in making a bipolar diagnosis at any age. Worrying is a completely different thought process than racing thoughts. Worry and racing thoughts can occur at the same time in susceptible individuals. While worrying is thinking about the same topic over and over again and is best treated with a serotonin based medication like Cielexa or Lexapro, racing thoughts are dopamine mediated and are best treated by use of a dopamine partial agonist or serotonin dopamine antagonist or Lithium. A thought process that jumps from topic to topic may account for the leap to complete optimism some people experience in which they perceive anything as being possible as the right non-dominant brain ceases to be analytical and instead puts together vaguely related thoughts together. Irritability and aggression is a secondary outcome of racing thoughts as frustration in the environment can result in an inappropriate jumping to a conclusion that someone is being slighted or disrespected. The jumping to a premature conclusion often seen in a people with racing thoughts who are being bullied or lied to is seen by both an adult and a child as an affront. Clearly both Lithium and Abilify or some of the other SDAs can be appropriate for the treatment of racing thoughts in young children and both have a large effect size. Long term treatment with lithium is supported by many years of data especially in kids whose parents have been successfully maintained on lithium. As time has gone on, diagnosing a classic bipolar person is getting less frequent and more mixed mood states complicated by recreational antidepressant use and substance abuse are being seen. The classic bipolar person who presented initially with euphoria and associated psychosis can be managed using monotherapy with lithium longstanding. There is the risk of kidney and thyroid challenges long term with lithium treatment yet many people have been able to be maintained on lithium as monotherapy well into their advanced years without kidney or thyroid complications using the lowest effective dose possible. Mixed episodes however seen in bipolar disorder are a complex series of symptoms described with difficulty. The outcomes for people with mixed symptoms can be uncertain and the CMRS can help sort these symptoms out. As pain and pleasure dopamine pathways become inefficient, a confusing mixed presentation of emotions can be seen. A person suffering simultaneously from low energy and racing thoughts at the same time does not have the same potentially good prognosis and positive response to lithium that a pure classic bipolar person may have.

Chapter Two
Psychopharmacology

Which drug to use first?
When someone is not helped by initial treatment with an antidepressant is when plan B is necessary. If someone presents in a crisis situation the decision of which medication to start can be a challenge. Ideally, the decision of which medication to start first is dependent on the severity, frequency of symptoms. Consideration of co-morbid medical conditions or the development of them should also be considered. While it may be that simply offering a serotonin histaminic and muscarinic acting dopamine antagonist may work abruptly and well for racing thoughts, it is important to consider the option of using a medication first that has the least risk of causing future metabolic syndrome at the onset of treatment. Medications like Zyprexa and Seroquel are easy to use and predictable however, these drugs do represent a possible challenge with future metabolic and cognitive challenges. Using a drug at the onset that has the least long term risk is the way to go. How this is done is where the art of medicine comes into play. A one time test dose of a long acting agent like Abilify with an excellent metabolic profile can provide a person with an

Page 27
The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
understanding that 10mg can work to instill a good night’s sleep and have an immediate effect so the person knows the medication is having some effect. This insight may lead the person to have better compliance long term at a lower dose as they know that a future cycling episode will respond to a higher dose in a predetermined way for a previously assessed period of time. This understanding can be emphasized by filling out the CMRS daily after a single test dose. Reviewing the rating scale daily can help someone develop an appreciation for the amount of improvement in thinking that initially occurs and may continue after 50% of the medication clears and symptoms start to return on the third day. Once symptoms start to reappear, the person is in a better position to understand the need for continuing treatment. I usually schedule a second appointment for this very reason on day three if the person can be placed in remission quickly. I can improve compliance by reviewing the pre and post rating scale surrounding the administration of a test dose with a person and a companion and demonstrating the observed change in symptoms. The benefit of the medication is usually apparent upon comparing the two rating scales and is emphasized by a return in symptoms after three days as they see for themselves that a return of their symptoms may be imminent. It is in this way that that compliance can be improved as the person has documentation in front of them that the medication worked for the symptoms they had. They begin to understand that if they continue to take the medication consistently, symptoms may not return. This demonstration comes at a price however. Medication blood level falls off 2 hours after a test dose and the person is not getting the full benefit of the medication as the dose lowers. This one time test dose procedure to help educate someone on the need for compliance requires that the clinician be available 24/7 by phone and be available on weekends in case suicidal thinking develops so that an emergency evaluation can be performed.

Each atypical antipsychotic is a unique molecule onto itself yet none of the atypical antipsychotic medications should be said to be weight neutral. Every atypical has the potential for weight gain though Abilify Latuda and Geodon in adults seems to cause less weight gain than the others. Zyprexa has a 1 in 25 risk of causing metabolic syndrome in 10 years and Seroquel has a 1 in 50 chance of causing metabolic syndrome in ten years. The risk of developing extra pyramidal symptoms is lowest with Clozaril, Zyprexa and Seroquel as these large molecules seem to bind transiently on the order of 16 seconds to a D2 receptor and as such do not tend to cause extra-pyramidal symptoms or movement disorder problems. They may be thought of as gently tapping a D2 receptor as opposed to binding in an irreversibly tight way to the receptor as the conventional antipsychotics do. The risk of tardive dyskinesia (TD) is still unknown with these drugs however, and only time will tell us the rates at which these drugs cause TD. Comparison of the new atypical antipsychotic medications with the older conventional agents is very hard to do because doses of the old conventional antipsychotic were comparably higher when compared with the doses used of atypical antipsychotics currently. Some people say that the risk of TD of the conventional antipsychotic was 5% per year and the risk with the new atypical antipsychotics is less than half that. Whatever the final verdict is on TD rates, it should be understood that until we have new classes of medications to treat psychosis we still only have D2 acting medications which need to be prescribed at the lowest effective doses possible to reduce the risk of future side effects. Risperdal seems to increase triglycerides selectively, Zyprexa and Seroquel increase lipid status across the board in many people. Abilify and Geodon have the best metabolic profile at this time. Time will tell if Saphris Fanapt and Latuda cause weight gain. An elevated blood sugar can occur independently of weight gain with all of the medications discussed. Lifestyle changes and diet is a must for anyone prescribed any of these medications. The warnings of these medications in the elderly speaks to the need for close follow-up and if used for behavioral...
disruption it may be worthwhile to stop the medication after 6 months to see if they are still needed as behavioral disruption can often be managed by behavioral methods without medications. If an elder develops severe extrapyramidal symptoms (EPS) on an atypical, it may speak to the person having a more severe level of underlying neurologic damage such as that found in Lewy body dementia and in diseases with both frontal and temporal deterioration. Much care must be taken in the use of these medications in people with dementia and psychosis and should probably be avoided unless other methods have been unsuccessful in treating their conditions. Difficult cases may require aggressive treatment yet aggressive treatment may incur some risks but not reckless risks. It is important to know that although the atypical antipsychotics can cause TD it is known that the ssris can also cause EPS in susceptible individuals.

The studies of the atypical antipsychotics improving cognition in chronically psychotic people has turned out negative. While we know little about how to pharmacologically grow brain in humans, we will learn more about this in the future. The only reproducible way we know how to make our hippocampus larger and improve our cognitive functioning is by exercise and cognitive training programs. Art Kramer at the University of Illinois Urbana-Champaign studied 65 year old people and made them exercise by walking 45 minutes three days a week for one year and found that the size of their hippocampus increased by 2 % on MRI scanning compared to age matched controls. He also found that their executive functioning improved by 20 % as well. The exact mechanism by which we can grow brain is uncertain. The cells in our brain have mitochondria just like our muscle cells do. We know that we can increase the number of mitochondria in muscle cells by long distance aerobic exercise and we know that having more mitochondria makes muscle cells more efficient and stronger. It is a reach to say that increasing the number and efficiency of mitochondria in brain cells helps cognition though it may be true that overall efficiency in a nerve cell may improve with an increased number of mitochondria. It may be that the brain cells work and respond in much the same way to a cognitive training load as muscle cells respond to a physical training load. Brain cells may take a longer time to respond to a work load stress. Antidepressants and lithium are thought to increase BDNF in adults. What we are left with is looking at particular symptoms to treat and using the current knowledge we have to guide our treatment of these symptoms with the lowest possible effective doses of medications to lessen the risk of potential side effects in the future and hope we grow brain as a secondary outcome. It is important to know that although increasing BDNF in someone's brain is possible with the medications we use, other processes are probably more important in restoring or improving functioning.

The Abilify partial agonist story
When a medication has 15 FDA approvals for its use, physicians take notice. When a medication like Abilify is approved for a treatment such as bipolar maintenance in kids ages 10 to 17 by the FDA without data, physicians really take notice. Aripirazole is a unique molecule and like all the atypical antipsychotic medications it has a pharmacological profile which causes it to stand out from the others. The term atypical antipsychotic is a very appropriate term as each compound is typically very different from the next. Abilify can be referred to as a 3rd generation atypical as its mechanism works by a partial agonist mechanism of action. The problem with Abilify is that it took years to figure out how to dose this medication most effectively. Abilify works very differently at a lower dose than at a higher dose. The reasons for why this medication may work differently at different doses may be related to the effects on cerebral blood flow that some dopamine agonists have. A low dose of this dopamine partial agonist functions as a weak stimulant clinically and at a high dose as a stabilizer. What constitutes a low and a high dose is variable dependent on a
person’s receptor density, severity of symptoms, co morbid medical problems and ability to metabolize the medication. While it is not active at D1, it does appear to be active in an energizing way by my observation and similar to the way a stimulant works clinically on a rating scale. Dopamine infusions used by urologist increase kidney perfusion at low doses, higher doses may reduce kidney perfusion. Abilify may be able to increase cerebral blood flow possibly in a manner similar to Amisulpride. Amisulpride is also a dopamine partial agonist as well. We know that Abilify acts as a partial agonist as it can reduce prolactin levels in people who have an elevated prolactin as a result of treatment with Risperdal. Abilify has a higher affinity for the D2 receptors in the hypothalamus and this enables Abilify to act as an antagonist to displace Risperdal and lower prolactin levels. Abilify also hits a D2 receptor for only 52 seconds then disengages. Other medications like structurally large molecules Seroquel and Clozaril do not appear to cause much in the way of EPS possibly by spending less time binding to a D2 receptor on the order of 16 seconds. Amisulpride is receptor bound for a short period of time as well on the order of 40 to 73 seconds. Abilify binds to a D2 receptor for about 52 seconds. The real question to be answered is if Abilify can stabilize a mood at a low dose of less than 5mg a day and it may not be able to as well as at a higher dose requiring continuing assessment and evaluation. The data I present will demonstrate that it is possible to stabilize a mood with Abilify and treat bipolar depression at a low dose less than 5 mg daily. To successfully do this requires personalized medicine, a combination of lifestyle changes, diet and often, a medication to improve DLPFC circuits.

Abilify is a D2 partial agonist and it has D3 action as well. It is similar to Geodon in that it causes little to no weight gain in adults most likely because it lacks the histamine H1 properties that other atypical antipsychotics have. Additionally, Abilify does not seem to cause dyslipidemia, increase fasting triglyceride levels or increase insulin resistance. Abilify is FDA approved to promote stability in schizophrenia and in the treatment of both mixed and manic episodes of bipolar disorder.

Abilify is not FDA approved to treat bipolar depression at a low dose. It did not reach the level of statistical significance necessary to receive FDA approval for this indication but most experts understand that a signal was seen in the study leading me to wonder if Abilify can be used to at least partially treat a depression or at least prevent a depression from coming on while other mood stabilizers or stimulants can be used to help prevent a depression as well including the use of cognitive behavioral therapy, exercise, and augmentation strategies other than antidepressants to keep people with cycling mood stable.

In my case series, Abilify was started at the lowest possible dose with the initial understanding that the dose would be increased over time. Higher doses of Abilify may be associated with tardive dyskinesia, elevated triglycerides and elevated blood sugars. Dose changes were made slowly over the course of monthly visits to give the receptors time to self regulate. While in general terms, it takes a short period of time to adjust mood stabilizers that work on voltage gated ion channels, it takes weeks to months for g-protein linked receptors to work to regulate receptors.

**Abilify dosing during the study**

Abilify has 2 metabolites with half-lives of 72 and 94 hours respectively. In my case series, Abilify was started in people who had mixed manic symptoms or manic symptoms with a test dose of 10mg once to assess a response then the dose was reduced down to either the original dose or...
to 2.5mg of the initial dose on a standing basis with the understanding that if an exacerbation occurred, that another one time dose increase to 10mg could be implemented with a following reduction. In my case series, Abilify was started at a low dose 2mg ¼ am in people who had low energy states as an augmentation strategy or as monotherapy in medication naïve people.

**Abilify doses used in the study**

1. Abilify 2mg ¼ tablet AM – starting and low energy
2. Abilify 10mg once – for manic or mixed manic state

In the FDA approval studies, Abilify augmenting mood stabilizers has been performed with higher doses and was well tolerated in studies without many complicating side effects except for akathisia which was associated with higher doses above 5 mg. Many of the people in my study population had multiple co-morbidities involving past head injuries and alcohol related toxicities to the brain making many of them intolerant of higher doses of antipsychotics. Augmenting mood stabilizers with low doses of Abilify in my case studies enabled people to successfully reduce doses of cognitive impairing benzodiazepines and mood stabilizers. Abilify in my population seemed to have modest antidepressant properties at a low dose below 5mg and was able to consistently induce a flat mood abruptly and at two hours at a high dose of 10mg once reliably. An infrequent one time extra Abilify 2mg ¼ dose was noted to be used by study participants to help ward off symptoms of anxiety and racing thoughts in as little as two hours and did improve insomnia. The mechanism of action by which Abilify at low doses increases energy levels is not known. My observation is that the restlessness which occurred in study participants appears to occur through a low grade akathisia-like mechanism of action probably related to action in the basal ganglia where people feel restless and feel like moving about but not to the extent that they are in distress in any way. The D3 receptor agonist action that Abilify has may predominate at lower doses. I found in the study that stimulants and wake promoters used to improve DLFPC subscale scores consistently improved the antidepressant effect of Abilify by 10%. Daily aerobic exercise increased energy in my population and augmented antidepressant action by 10% as well. Deplin was not used in any study participant.

**Why low dose Abilify?**

1. I used low doses of Abilify in the study population because of intolerance to higher equivalent doses of other atypical antipsychotics,
2. Past history of head injury, neurologic trauma and alcohol blackouts
3. There is some evidence showing that even low dose of atypical antipsychotics have a risk of TD as seen in Risperdal and Zyprexa in the elderly. It intuitively may be that a lower dose of Abilify may confer a lower risk of TD but further study will be necessary to prove or disprove this theory. Using the lowest possible effective dose to minimize the risk of side effects is what we all wish for in treating our patients. A self rating scale is a tool that can help us do this with a minimum of wasted time, effort and energy by placing some of the responsibility of care back on the patient letting them quantify their response to treatment and having them demonstrate the usefulness of the medication.
4. D3 activation at lower doses?

In the early 1990s, mixed mood disordered people were treated with low dose Risperdal 0.125 mg to 1mg and Depakote 500mg to 1500mg to treat moderate mixed manic symptoms. The idea was to enable the person over time to find out which medication helped treat depression and mood swings better. The idea at that time was to try to find medications which would not promote mood cycling while helping improve energy and sleep. Risperdal would act at a low dose to give...
energy and Depakote was used to help with sleep and mood at night. I saw this clinically to work quite well for many people but the antidepressant effect was not that great and most people had to augment these medications with exercise.

Clinicians are blessed with having a tool such as Abilify which appears to be at this time safer than many of our other tools to treat people with cycling moods. Understanding how this tool is used most effectively with its long half life is challenging. Learning how to control neurons and synapses as best we can effectively until other safer tools can become available is the best we can hope for at this time.

In order to reduce the mood stabilizer dose of the study participants, I decided to use as an augmentation strategy the lowest possible starting doses of atypical antipsychotics possible. This meant taking the smallest Abilify 2mg tablet that it comes prepared at and dividing it in quarters. Thankfully the binders and fillers that hold the tablet together are of a superior quality so that they did not shatter and can be snapped and cut precisely on the rounded edge of a table without a pill cutter. A Geodon 20mg capsule is the smallest capsule available and once it is opened into a cup of applesauce and stirred, 50% was consumed to deliver a 10mg dose.

Newer antipsychotics are being developed which may have an even better side effect profile in the future. Each of the atypical antipsychotic medications has a unique complex pharmacology as they are multifunctional medications having different effects and properties at different doses. Abilify may be used safely to augment or improve symptom response to antidepressants and mood stabilizers like lithium and Valproate, when remission or complete improvement has not occurred. All of our currently available antipsychotic medications work to treat psychosis by blocking 70 to 80 % of dopamine receptors for 2 hours a day. The newer agents do this in addition to having other unique actions. Abilify is called a dopamine partial agonist and to understand how this medication works distinctly from the other atypical antipsychotics requires an understanding of the manner in which nerve cells communicate with each other.

Abilify is a dopamine partial agonist which means that at a low dose, this medication increases the resting state firing of a neuron above baseline. Abilify modulates nerve cell firing and it may not allow a neuron to fire in a phasic or alerting manner if dosed high enough. Abilify is best looked at in this way as a stabilizer of dopamine neurons throughout the brain and it is useful in treating many of the symptoms that people have when they are acutely in distress and are having orbito frontal pathway deregulation seen on page one of the CMRS which is an abbreviated Young mania rating scale. Page two on the CMRS is an ADHD rating scale and page three a toxicity screen for mood stabilizers. Adjustment of medications using the rating scale is based on minimizing OFC symptoms, maximizing DLPFC efficiency and minimizing side effects on mood stabilizers. Varying the doses of a partial agonist is complicated and important as it provides an opportunity for optimal regulation of a mood disorder with little risk of metabolic complications. The partial agonist of a dopamine receptor allows for a net increase in firing of the nerve cell at a low dose, and at a higher dose, the effect is to block the receptor like an antagonist does and reduce the frequency of firing to a baseline level. So, stated in simple terms, a dopamine partial agonist like Abilify will increase firing like an agonist at a low dose and will decrease firing to a baseline level like an antagonist at a high dose. An antagonist blocks the action of an agonist medication such as a peptide or steroid and reduces firing rate back to baseline. The concept of an inverse agonist is one in which a medication will bind to a receptor to cause a conformational change in the receptor causing an action opposite to the effect of an agonist.
A dopamine partial agonist can be used to modulate dopamine pathways that are either firing too excessively or are not firing enough by varying the dose administered. Someone whose firing rate of dopamine neurons is excessive will appear anxious, hyperactive and may be impulsive. A high dose of Abilify at 10mg may enable a net decrease in this firing rate and a state of relaxation can occur. If someone presents with a low rate of dopamine firing they may appear to have low energy, yawning, and have trouble concentrating as their level of arousal is low. A low dose of Abilify in this same individual in my study population at Abilify 2mg ¼ am provided motivation in the form of restless energy to enable someone to accomplish something that they need to do by causing a net agonist or increased firing effect. The other way to look at how a partial agonist works is by using the analogy of a light dimmer switch on a chandelier. A dimly lit room can be made brighter by turning on a rheostat set on a dimmer switch turned up a little. A brightly lit room can be darkened by turning the switch on which has been turned down a bit. Abilify acts as a dimmer switch which can be turned up or down to give a net positive or net negative effect on dopamine neuronal firing. The net firing rate however, is dependent on where the original state of neuronal firing started from. We have many other partial agonists available to us to use in addiction medicine at opiate and nicotinic receptors and they work essentially in a similar manner by modulating firing tone. Deep brain stimulation for the treatment of chronic pain and movement disorders is thought to work by modulating dopamine neuronal tone.

Abilify is a multifunctional drug
The emotional functioning, worrying and obsessing subscale scores can be improved with the use of multifunctional medications such as Abilify at an appropriate dose in many people. A one time dose of Abilify which blocks 70 to 80% of D2 receptors in the mesolimbic pathway enabled reduction in frequently occurring symptoms in these subscales in as little as two hours. The dose given needs to be tolerable such that it should not cause headaches or nausea however, it should provide a noticeable response for the person so they know that the medication has an effect. Having a first dose effect is extremely important as a person is more likely to take a medication if they can observe a response. The people in the study population needed to know that the medication would predictably have a given effect on them when they need to step up to perform at a high level. Having this knowledge of what a medication can do to improve certain symptoms can help save relationships and careers during high stress times. This knowledge is also the way that we see improved compliance in taking medications. People who have suffered from multiple head injuries or a traumatized brain caused by alcohol use, generally seems to require lower doses of an atypical antipsychotic as maintenance therapy. A person with a large liver or with a supercharged liver enzyme system will generally require higher doses. Abilify is not very sedating by itself at doses between 2 to 5mg a day as it has a low affinity for histamine and alpha one receptors. There are however, some individuals who will become rarely sedated on it and a few will gain weight. High doses of Abilify can cause restlessness, headaches and nausea given continuously. A one time test dose of 10mg often does not cause these symptoms and has some predictive value as to how someone’s dopamine system will respond to a dopamine acting medication. A well tolerated higher one time dose of Abilify may give some insight into how the medication may work at a lower dose. It is rare that someone will have intolerable restlessness on a low dose of Abilify but it is always possible as it does work as an agonist at lower doses. It is also rare that someone will have a worsening of psychosis on this medication but this is theoretically possible as well. A low dose of this partial agonist may increase firing in the mesocortical pathway causing an increase in alertness if the prefrontal circuits are relatively low in dopamine firing. If the attention concentration and executive functioning scales are high, a low
A lower dose of Abilify less than 5 mg may be able to treat a low energy mood state somewhat as evidenced by studies. It is important to know that these studies did not reach a level of statistical significance necessary for the FDA to give approval for the drug to be used in bipolar depression however. Many people with mood swings who have elevations in their emotional functioning and worrying and obsessing subscale scores were managed in the study population with low doses of Abilify and were given a stimulant or wake promoter in the morning to help improve their cognitive functioning in lieu of using caffeine or coffee. People who have had a chronic course of having multiple low energy states treated with antidepressants may still require antidepressant treatment indefinitely. There is always the risk of mood instability in people taking antidepressants who have a cycling mood. It does not appear that stimulants cause a cycling mood as the antidepressants do. Low dose Abilify started initially with its long half life takes several weeks to reach a peak plasma level. Care should be taken to avoid having a person develop a flattened mood as a result of frontal lobe reduced firing as Abilify at a higher dose acts as an antagonist and can leave some people with a flat blah mood state weeks out from a dose that may have initially worked well. When using Abilify as add on agent to antidepressants, it is important to use a low dose initially. If the dose is started too high initially, a flattened zombie like mood can develop requiring the dose to be cut in half. Often this will result in a brightening of mood over the course of a few days as the antagonist effect is lost and the agonist effect takes over. The risk of akathisia in a middle age population is probably greatest using Abilify at doses above 5mg daily.

The one time test dose
There are many reasons to use a one time test dose of a medication in a person with either a first time psychiatric illness or a recurrent illness. Often the information made available to us as physicians may not be as reliable as it could be and complicating variables such as substance abuse are simply lied about by patients. Compliance with medication treatment is also suspect in people. While we do not want to over medicate we also do not want to under-medicate. We want to demonstrate to a person so they can see for themselves that a medication has a specific effect that is desirable and we want to avoid untoward side effects. A one time test dose can provide an opportunity to demonstrate to a person that symptom improvement can be accomplished at a specific dose to a specific reproducible degree. Abilify at 10mg owns 70 to 80% of a receptor and will displace a stimulant medication to improve untoward side effects or behaviors caused by excessive use of a stimulant. People have varying degrees of sensitivity to medications based on many factors including receptor density and sensitivity. In my practice I have seen people have sensitivity to atypical antipsychotics sometimes based on a past history of closed head injury and alcoholic black outs. I recommended that a low dose of Abilify be used initially so as to allow for a reduction in the side effect burden of mood stabilizers by dose reduction. Someone with severe symptoms that are occurring more than 90% of the time and are interfering with functioning may need a 10mg Abilify test dose to have improvement in symptoms and functioning documented. It is important to be able to know how to shut down a brain under stressful situations and it is equally as important to know what side effects a person may develop in response to a test dose. If anxiety hand tremor and panic improves then a 5HT1A partial agonist like buspar or 5HT2A antagonist acting medication may help the person in the future. In the cases I have reported here, the test dose was used to help acutely dysfunctional people become functional in an emergency situation when the severity and frequency of symptoms was extreme and life threatening. Abilify, as mentioned previously, displaces Risperdal, Haldol and stimulants with a high affinity for 70 to 80% of D2 receptors at a dose of 10mg.
Reasons to use a one time test dose of Abilify at 10mg off label

- When the sedating effects of Zyprexa and Seroquel would not be tolerated
- Averting an acute hospitalization
- When prior knowledge of side effects and level of reduced arousal is associated with a one time top end dose for time zone travel is required
- Prediction of response to Abilify in the long term
- Differentiating ADHD symptoms vs. pure bipolar agitation vs. anxiety induced tremor
- Treatment of acute panic and suicidal ideation
- Ensure compliance when given in the office accompanied
- Manages acute depressive states for 3 days over the course of a weekend
- Use in an emergency situation before initiation of an SSRI for a unipolar mood state as a pre-augmentation strategy
- Use to calm agitation of people on high dose Zyprexa/Prozac
- Use to calm agitation in people suffering from agitation due to stimulant misuse
- Reset dopamine set point after medication deregulation

Antipsychotic drug potency Manual of Clinical Psychopharmacology
Schatzberg 2010

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Chlorpromazine equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>Abilify</td>
<td>10mg</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>Thorazine</td>
<td>100mg</td>
</tr>
<tr>
<td>clozapine</td>
<td>Clozaril</td>
<td>50mg</td>
</tr>
<tr>
<td>fluphenazine HCL</td>
<td>Prolixin</td>
<td>2mg</td>
</tr>
<tr>
<td>haloperidol</td>
<td>Haldol</td>
<td>2mg</td>
</tr>
<tr>
<td>loxapine</td>
<td>Loxitane</td>
<td>10mg</td>
</tr>
<tr>
<td>molindone</td>
<td>Moban</td>
<td>10mg</td>
</tr>
<tr>
<td>olanzepine</td>
<td>Zyprexa</td>
<td>~5mg</td>
</tr>
<tr>
<td>perphenazine</td>
<td>Trilafon</td>
<td>10mg</td>
</tr>
<tr>
<td>prochlorperazine</td>
<td>Compazine</td>
<td>15mg</td>
</tr>
<tr>
<td>quetiapine</td>
<td>Seroquel</td>
<td>63mg</td>
</tr>
<tr>
<td>risperidone</td>
<td>Risperdal</td>
<td>0.5mg</td>
</tr>
<tr>
<td>thiothixene</td>
<td>Navane</td>
<td>4mg</td>
</tr>
</tbody>
</table>

How to use the CMRS to reduce augmentation medication doses

The CMRS functional scale at the top of page one documents both a need for treatment and the degree to which someone perceives themselves to be dysfunctional at work/home or in relationships. As a self rating scale varies dependent on insight it is important to have a third party validate the patient’s rating scale to see if the answers are an accurate representation of what is observed by another concerned person. It is important to understand to what degree improvement in overall functioning can occur when medications are adjusted. It is also important to understand that recovery is a slow process when someone has been dysfunctional for a long time. If someone has had their antidepressant augmented with Abilify, they should generally be...
maintained on the drug for a period of one year in remission before a dose reduction is attempted unless you have a set of parameters or a bio-marker that suggest that their neural networks have improved in their efficiency sooner. People who have insulin dependent diabetes know that stress on multiple levels can cause their blood sugar to elevate. There are people who find that despite being on an antidepressant, they may have breakthrough low energy states occur at times and they may also find that augmentation with a medication like Abilify or Geodon will lower their blood sugars as it helps them cope better with stress. Once started on Abilify in augmentation, many symptoms on the CMRS get better. There may be some instances such as in the treatment of people with an elevated blood sugar where a more rapid reduction may be considered. If a person with diabetes develops an elevated blood sugar because of the stress of having a low energy state, many people started on low dose Abilify or Geodon with an antidepressant have an improvement of their blood sugar in 4 months as the stress of their low energy state improves. This reduction in blood sugar I have taken as a sign that the person’s stress hormone levels have self regulated with treatment over 4 months of augmentation therapy and I was able to slowly taper and stop the augmenting atypical antipsychotic. During this time, combination therapies of excellent diet, weight loss, exercise, and therapy as well as mindfulness training may be able to promote further healing and facilitate a reduction in Abilify or Geodon dose. Once functioning is optimized over the course of a year and behavioral methods are utilized to keep the person in remission and functioning at a high level, a slow reduction in Abilify can be attempted first with a onetime dose reduction waiting a one month, then with a 10% sustained per month reduction or slower. A mood which has been flattened as a result of higher doses of Abilify being used may require a faster reduction by half and use of another augmentation strategy such as another antidepressant agent, monoamine oxidase inhibitor or stimulant to maintain energy levels. It is important to understand that there is very excellent long term data available showing that antidepressants shine by preventing low energy mood states from returning in people who have had recurrent low energy mood states but can make people with cycling moods worse.
### Medication risks vs. benefits chart for medication management

<table>
<thead>
<tr>
<th>Relative effective dose</th>
<th>Medication one</th>
<th>Medication two</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keep dose the same</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevate dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The use of the *Risks vs. Benefits Medication Chart* is important in figuring out if a medication is causing a side effect. The medication that is at the highest effective relative dose relative to others is usually thought of as being most likely to be causing a side effect of concern. The medication can be adjusted downward one time to see if the side effect goes away. As a general rule, one side effect can reduce a dose of a medication of concern by 10% and 2 side effects can lead to a 20% dose reduction. If a one time dose reduction occurs without problems in functioning, wait one month then start a sustained reduction over the next month. Here are some tables describing various side effects that are generally seen with various medications at higher doses.
Antidepressant side effects which respond to dose reduction

- Nausea
- Diarrhea
- Rapid cycling mood
- Zombie like feelings
- Agitation/irritability
- Sexual dysfunction
- Headaches
- Restlessness
- Diarrhea
- Sweating
- Flattened mood and anhedonia
- Cognitive problems
- Movement disorder
- Lowered sperm count
- Insomnia
- Weight gain
- Fatigue and somnolence
- Tardive Dyskinesia
- Swaying
- Unpredictable bleeding and thrombosis risk

*It is appropriate to increase levels of antidepressants to try to improve a response but the fact that 90% of serotonin receptors are in the gut and not the brain can cause side effects.

Mood stabilizer side effects

- Word finding and switching
- Simple math problems
- Nausea
- Vomiting
- Diarrhea
- Sensitivity to bright lights
- Sensitivity to loud noises
- Tremor
- Agitation insomnia or hypersomnia
- Rash
- Weight gain
- Fatigue
- Hair loss

Page 3 of the CMRS can steer prescriber’s to appropriately reduce doses of mood stabilizer medications without risk of mood cycling if appropriate augmentation is used.
Benzodiazepine side effects

- Muscle weakness
- Fatigue
- Memory loss
- Poor attention and concentration
- Slurred speech
- Reduced arousal
- Disinhibition
- Coordination problems
- Somnolence
- Dizziness and lightheadedness
- Slowed reaction time

Benzodiazepine side effects may be treated by alpha 2 delta ligand substitution with medications such as Neurontin gabapentin and Lyrica pregabalin. Akathisia and anxiety may also be treated by gabapentin and pregabalin off label instead of using benzodiazepines.

Side effects on Zyprexa/Seroquel

- Weight
- Somnolence
- Sedation
- Constipation
- Cognitive problems
- Increased abdominal girth
- Muscle weakness
- Excessive sleepiness
- Calmness
- Excessive relaxation
- Triglyceride elevation
- Cholesterol elevation
- Blood sugar elevation
- Metabolic syndrome
- Swelling
- Extreme hunger
- Tardive dyskinesia
- Restlessness
- Fatigue

Switching from one atypical antipsychotic to another is an art form which requires slow and careful consideration of dosing, half-lives and watching for rebound and withdrawal symptoms. Abrupt switching is neither recommended nor advised.
Lamictal general indications for use

- 3 generations of mood disorders
- 3 failed antidepressant trials
- Diagnosis of Bipolar two
- Few and far between hypomanic episodes
- Progressively longer periods of depression
- Previous side effects to antipsychotics or antidepressants
- History of closed head injuries concussions
- Blunt head trauma
- Coronary artery risk factors diabetes, hypertension smoking elevated cholesterol stroke
- PTSD symptoms
- History of cutting
- Family history of bipolar one
- Extreme anxiety
- History of self-destructive acts

Lamictal has changed the way many psychiatrists practice psychopharmacology. For many people this medication has been life improving. Slow titration to avoid a potential Steven's Johnson Syndrome rash is very important. Aggressive dosing can occur when Lamictal is used in conjunction with a CYP 450 inducer like Tegretol and slower titration needs to occur when Lamictal is used with a CYP450 inhibitor like Depakote. At higher doses however, Lamictal can cause cognitive problems such as blurred vision, double vision headaches and dizziness.

Lamictal side effects above 200mg

- Nystagmus
- Double and blurred vision
- Headaches
- Nausea
- Dizziness
- Lightheadedness

The use of medication augmentation agents and monitoring

L-methyl folate and omega 3 fatty acids are now recognized as being add on agents to antidepressants in treating low energy mood states and have a level of clinical confidence below that of Abilify augmentation. Both of these substances are thought to work at the level of gene expression to improve mood. We know that folic acid cannot cross the blood brain barrier and...
folic acid is converted into L-methyl folate. L-methyl folate is available as Deplin which methylates the gene in DNA which codes for the production of catecol-o-methyltransferase the enzyme that degrades dopamine at the synaptic cleft in our prefrontal cortex. Carriers of the VAL VAL phenotype have 400 times greater COMT activity than the MET MET phenotype and we can see on fMRI scanning that the MET MET people are more efficient at doing cognitive tasks than VAL VAL people. Many foods are methyl donors and as such have the ability to help us live more healthy lives. Omega 3 fatty acids have also been shown to act as anti inflammatory agents and are a required nutrient. The advantage of using a food supplement such as Deplin to increase prefrontal dopamine levels is that there are no known side effects at this time. Adding another antidepressant or Lunesta may enable a reduction in an atypical antipsychotic used as an augmentation strategy. To know if any of these add-on strategies are helpful for cognition however requires the monitoring of mood and cognition on the COLORADO mood rating scale and needs to be done daily.

Improving cognition and strengthening the brain
Every person who is interested in improving cognition needs to be able to buy into using a self rating scale as a way of tracking symptoms. The mind is a process that regulates the flow of both energy and information in the brain. Learning occurs simply by filling out the rating scale daily and some may say that improvement on a rating scale automatically happens when we fill out the rating scale daily. My answer to that is that a necessary part of cognitive improvement is the asking of questions everyday to help us focus on improving cognition. We think by asking ourselves questions all the time. These questions focus our thinking and this is how we improve our thinking. We do not spend as much time thinking about thinking as I think we could. We do not spend as much time thinking about helping our children’s thinking as we should. I believe that a self rating scale improves insight by focusing our attention on our thought process. Filling out the rating scale can be done within 3 minutes. The state of mind that is accomplished by focusing our thought process on our thinking may develop into a trait over time and increase our ability for insight either because words escape them or they have little insight into their own emotional experience. For these people, having a 60 question document which expresses what they are experiencing may help a provider of care quantify the degree to which someone is experiencing key symptoms and how much improvement they may be getting from particular treatment. The good news is that the simple act of self observing or asking excellent question of ourselves everyday promotes change which may occur independently of medications. Asking ourselves positive questions and using a positive word vocabulary will help people improve their low energy mood state if done effectively. As one becomes a master of improving ones mood by movement, vocabulary and directed thinking, the CMRS can be used to guide a reduction in medications dependent on the subscale scores noted by the person being evaluated or a concerned caretaker. It is very important to know that changes in medications can take weeks to cause an effect as neuronal structure turns over slowly about every 4 months. Receptor down regulation as a result of antidepressant treatment takes 4 to 6 weeks. Studies in cognition take years to do as a result of slow neuronal cell turnover and the benefits of the psychotropic medication improving cognition in people with schizophrenia have not been outstanding. We know that we can improve processing speed, in people using some medications. Improving semantic and episodic memory is more of a challenge. You have to have a brain that is capable of making new neuronal connections and circuits in order to self assess the appropriateness of social interaction real time in both verbal and non-verbal ways in order to function in the work place. Being able to assess the appropriateness of social interaction real time in both verbal and non-verbal communication between two people, really determines functioning in relationships at work and our ultimate
outcome. Improvement in this complex area of human interaction is hard to measure. Continually asking ourselves questions about the appropriateness of our interactions with others is exhausting work. Self assessment needs to be done regularly in order to improve overall functioning. Therapy and mindfulness meditation can help with social interaction as can going over in our mind our interactions with others regularly. A separate set of questions in the form of a rating scale can be used to look at this aspect of human interaction directly which may include am I listening to others carefully? Am I sensing others non-verbal cues accurately? Am I empathic with others? Am I understanding others thoughts, emotions, intentions and feelings? Am I able to present myself to others effectively and can I predict and shape the outcome of social interactions? Active listening requires focused attention and a fully functioning auditory system. Many times a relationship does not succeed as a result of hearing problems and a complete physical examination and hearing test may need to be done. If any of our senses of perception are not completely operational we can have challenges with the language and communication subscale, The language and communication subscale can be an indicator of subtle drug side effects especially secondary to anti-seizure agents which are often used in combination therapy to treat mood symptoms. Having someone read complex technical information and dictate into a recording device for later review can improve verbal fluency, spontaneous recall of information, and can challenge the brain to adapt to a new stress and promote learning. Training the brain in this way can promote an improvement in self esteem and can lead to someone doing better in job interviews or standing up for themselves in relationships where they may feel disregarded. Training of the dopamine pathways in this way is hard work and can be rewarding. Careful attention to cognition and its multiple facets is complicated and can pay off in the long term in helping us improve our results. The use of a tape recorder for dictating and listening to one’s own voice can help someone understand how they may appear to others and can help with presentation skills. In an age where communication of highly technical material in an understandable way is valued at a premium, training in this area can be very helpful for gaining new employment by promoting one’s self. Listening to the fine nuances to the voice inflection that others have requires our attention, concentration, and auditory circuits to be as efficient as possible. Medications that help increase dopamine firing in the frontal lobes increase attention concentration, processing speed, and improve signal to noise ratio. The stimulants, such as wake promoters, alpha 2 agonists such as Guanfacine ER all help with attentive listening probably by increasing signal to noise ratio.

Signal to noise ratio
The signal to noise principle is best understood by the phenomenon which occurs when you are having a discussion with a single person in a loud and crowded Chinese restaurant. With low frontal lobe dopamine firing, attention and concentration is low and it is difficult to separate out the background noise from what the person in front of you is saying. However, when there is plenty of frontal lobe dopamine, it is easier to understand the person because you can separate out what
the person is saying from the background noise. Insight into solving complex problems requires a quiet mind to identify subtle dopamine firing patterns that can give us new ways of looking at problems. Meditation and focusing on the breath develops a calm trait that with practice develops into an enduring state. Medications are specifically designed to do this but there is an art to understanding the level of arousal someone needs in order to have an improved signal to noise ratio. Too much of a good stimulant can lead to excessive firing in pathways other than the prefrontal cortex and insomnia, hand tremor and body shakes can result as well as weight loss from a decreased appetite. The frontal lobes need a certain amount of baseline neuronal firing in order to be able to react to stimuli that they may encounter. A tennis player keeps his feet moving at all times while returning a serve so that he may engage the dopamine system at a moments' notice. Similarly, swimmers on the starting blocks clap their hands to energize their dopamine system and prefrontal cortex to help them get off the start faster. A determination of an under arousal state vs. over arousal state in an individual in a psychiatric practice is important. Falling asleep in a classroom is typically caused by being in a state of under arousal and learning under these circumstances can be challenging. Excessive anxiety can cause challenges with learning as well. A dopamine stabilizer such as Abilify can regulate the flow of energy and information processing in a system which needs to adapt to ever increasing demands of a changing environment. If someone's set point has been dramatically changed by drugs or alcohol a one time Abilify test dose may reset this system for a period of time allowing for regulation.

Any medication that causes fatigue will reduce arousal and interfere with attention, concentration and learning. The challenge with improving cognition while treating mental illness is to use medications that do not cause fatigue or sedation. If we have to use medication to treat our people that cause fatigue or sedation we should use them at a low enough dose that side effects do not show up on a rating scale or are noted by others. Another way of assessing the degree to which a medication is causing side effect challenges is using the visual perceptual sub scale. If someone is in a hyper vigilant state, they may be more sensitive to excessive environmental stimulation and as a result suffer from excessive neurotransmission. A hyper aroused state long term can cause undue stress on the hypothalamic-pituitary-adrenal axis and can cause atrophy of the hippocampus. We are designed to learn under a moderate amount of stress. A great deal of stress impairs our ability to learn. An acute increase in stress level causes an acute increase in cortisol and makes encoding our memories easier. Prolonged high cortisol levels seen in prolonged hyper aroused states can cause a reduction in memory functioning. Medications that help improve the thalamic filter such as anti seizure medications can enable someone to reduce their level of perceived stress by filtering out excessive stimulation and can improve the hypothalamic-pituitary-adrenal axis. Excessive prolonged exposure to bright lights and loud noises can lead susceptible individuals to inadvertently use higher levels of medications that shut down the brain through augmenting thalamic filtering than they should and this can be assessed on the CMRS. Excessive use of thalamic filtering medications such as anti seizure agents or benzodiazepines can lead to problems in cognitive functioning is seen especially in the communication subscales. While we would like to think that all stress is bad and if we could entirely avoid stress we would be free from emotional fallout, this is not necessarily true. We are by design adaptive creatures that need stimulation on a continuing basis for us to grow and prosper. If we are cut off from stimulation, our thinking diminishes. The major way we learn is through our visual system. Myelination starts at the back of our brains at an early age and this process moves forward to our frontal lobes to speed the rate of neuronal transmission. It is intuitive that we may be able to facilitate this neuronal development by eating a diet rich in omega 3 fatty acids and avoiding fast foods however, this has yet to be proven. High scores on the visual...
perceptual subscales may also indicate sensitivity to sensory stimuli which can suggest a subclinical seizure disorder. The risk of having subclinical seizures is increased with a history of head injuries, brain infections, and stroke. In the future, it may be that metabotropic glutamate acting medications may be helpful for modulating neuronal circuits in people with a chronic psychotic condition to improve their cognition and a baseline level of sensory sensitivity using a scale may help guide a clinician in assessing improvement or worsening of these symptoms or the development of side effects using these medications.

I am not sure if the relaxation that occurs with an increased level of frontal lobe dopamine is responsible for taking the burden off of hypothalamic fear circuits and toning down worry circuits. It may be that an improvement in neural network frontal lobe efficiency may help the frontal lobes dissociate from the limbic system during sleep. Improving frontal lobe efficiency may improve the frontal lobes drive inhibitory input into other areas of the brain. Stimulants seem to relax motor pathways in attention deficit disordered people by making cortical neuron projections more efficient and taking the load off of the hypothalamic-pituitary-adrenal axis. This may be why it is impossible to worry while you are exercising. Taking the load off of the hypothalamic-pituitary-adrenal axis circuits by redirecting information processing to striate neurons makes it difficult to worry while exercising. It is unclear to me if medications work in this same way to redistribute load or they may make circuits more efficient at doing the job that they were designed to do. Clearly circuits can be overloaded and constant work stress can be relieved by alternating load to different circuits. If a stimulant medication does cause insomnia however, it can tax an already overused hypothalamic circuit. Guanfacine ER seems to cause sedation and relaxation and can increase adrenergic neuronal firing by agonist action at alpha 2 A receptors to improve attention concentration and focus. Clonidine is also an Alpha 2 agonist but is more non-specific than Guanfacine ER is.

How to manage a cycling mood state with Abilify

I offer these five guidelines for the treatment of managing a cycling mood state with Abilify:

1. Use the lowest possible effective dose.
2. A rapid response in a rating scale with an Abilify test dose may portend a potentially a good response to Abilify in the future if they are in a high energy state.
3. Poor initial response to a one time 10 mg dose may mean that the medication will not work or is poorly tolerated.
4. Lower doses of Abilify below 5mg tend to treat a low energy states
5. Higher doses treat high energy hypothalamic-pituitary-adrenal axis states and a one time dose of 10mg or higher can put the brakes on insomnia and racing thoughts in responsive people.

The benefits of using Depakote are that it can help with irritability mood cycling and substance use in both Type one and two people with a history of head trauma and seizure problems. The down side of Depakote is that there are cases of reduced IQ in children whose mothers were on Depakote during their pregnancy. The atypical antipsychotics seem to be gaining wider acceptance for this population of young mothers because of the anti -seizure agent Valproate having the potential for causing low IQ in offspring in young woman of child bearing age. The anti
seizure medications work quickly through voltage sensitive sodium channels and can have a rapid effect on cognition as evidenced on a cognitive screen like the CMRS and can cause neural tube defects in developing children. The atypical antipsychotics work through a slower mechanism of action namely g-protein linked receptors that have slower effects on neurons through protein kinases which over the course of days and weeks can regulate receptor number and sensitivity and do not seem to be correlated with causing birth defects with the information available at this time. The exact mechanisms by which medications increase BDNF and other brain growth factors are not precisely known at this time but will be known in the future. In general, it is important to note that in studies of people taking conventional antipsychotics there is a generalized enlargement of the basal ganglia and a relative atrophy of the hippocampus. When conventional antipsychotics are stopped and atypical antipsychotics are started, the basal ganglia gets smaller and the hippocampus enlarges suggesting that synaptogenesis may be increased by the atypical antipsychotics possibly through a 5 HT2A antagonist mechanism of action which many of them work through. Until such time as we can utilize PET scanning to improve our recommendations regarding doses and drugs, we are left with trying to assess symptoms by way of self reflection scales, symptoms and severity. Eventually biomarkers will be developed to help guide medication recommendations. Until biomarkers are proven to be helpful, we are left with a clinical interview to assess diagnosis and a rating scale to quantify treatment response. Current biological markers which may prove useful include cortisol levels, blood sugar levels in diabetics, homo-cysteine levels, and the genetic markers for COMT and methyl tetra hydrofolate reductase as well as other genetic markers.

How to treat bipolar depression
Bipolar disorder is an illness that starts at an early age and manifests mood swings of mania in a high energy mood state and at times manifests low energy mood states. The criterion for bipolar disorder for children is currently being revised in DSM5. The criteria will most likely focus on irritability as a major key symptom associated with racing thoughts as part of the criteria needed to have a diagnosis of bipolar disorder. The problem of having a chronically low energy mood state is very problematic for people who have bipolar disorder and is very difficult to treat. Lithium is one of the two medications available which has been shown to reduce suicide in people with mood swings. Many people with mood swings who are creative may fear that medications will take away their creativity. It is possible to manage medications so that creativity is not affected and that people can lead long and productive lives. We know that Seroquel is FDA approved for the treatment of bipolar depression and a combination of Zyprexa and Prozac are used to treat bipolar depression. Both Seroquel and Zyprexa have an increased risk of weight gain and metabolic syndrome. Abilify at a low dose seemed to help depression associated bipolar disorder at a dose below 5mg daily in phase 3 studies though it did not reach the level of clinical significance enough for it to gain approval by the FDA. The high affinity Abilify has for D2 receptors may selectively cause it to bind to sub cortical D2 receptors slowing racing thoughts in the meso limbic pathway. Medications that have been shown to improve dorso lateral prefrontal cortex functioning are the stimulants, atomoxetine and Guanfacine ER as well as Nuvigil and Provigil. These medications can be given with low dose Abilify to improve mood and cognition and the additive energizing effect of these medications may prevent a depressive state. Antidepressants have not been shown to reliably improve mood in people with bipolar depression and some groups feel that there is an excessive risk of mood cycling with antidepressants. Lamictal has changed many physicians’ practices as it has been able to stabilize people and give them the energy they need to function when they suffer from low energy states associated with bipolar disorder and Lamictal does not appear to induce mood cycling. Saphris has a structure
similar to Remeron and Latuda has been shown to have effects through a 5HT7 mechanism of action which many antidepressants work through.

Evidenced based medicine treats an easy to treat patient population though can be a dilemma for many physicians whose patient population is not representative of the patients treated in phase 3 clinical studies needed for FDA approval of medications. We would all like to see the positive evidence that a medication works before starting a treatment to know that it will work without side effects. We know that there is always a risk of side effects and no guarantee that a particular treatment will work for a particular person. We can say based on clinical studies that we know with 90% confidence levels that a person with a particular set of symptoms will respond to a medication intervention. The studies that medication trials are based on however include a population of people who most clinicians would consider pristine being that they have no co morbid personality disorders, no substance abuse, and are compliant with medications all of which may not be true in our standard clinical practice. What constitutes evidenced based medicine is variable. It maybe a combination of randomized trials, case studies and case reports that constitutes our standard of care. It may be randomized clinical control trials and information from experts. What primarily determines how a physician treats a person is based on a clinician's own experience with treating people with medications in the past and learning what works and what does not work. While there are many guidelines that are available to guide us in our decision making, the way we perceive what a person needs for excellent health and their longevity plays a pivotal role in the determination of how we treat people as well. Evidence based medicine has been described as a bridge between research articles that give us information and clinical expertise which enables us to treat people with the best possible medical care available. Clinicians value traditional skills of diagnosis and treatment and the systematic asking of questions to give us mathematical estimates of risks and benefits to obtain the best possible results for people. We now have access to data bases such as Pub Med so that we can get answers to questions. Every one of us has questions which we need to know the answers to so we can make the best possible decisions regarding our people. Physicians make decisions in the face of uncertainty and weighing out the risks vs. benefits is something we do a lot of. We make life and death decisions every day as prescribers and therapists all the time. How we make these decisions is based on the data we have in our hands at any given moment. Our skill as observing physicians plays a large role in our ability to attend to the needs our people have. Evidenced based medicine provides us with a clear understanding of what we need to do in order to provide the best care possible with a minimum of risk. In an information based society, clarity needs to be separated from uncertainty. It would appear that the information we have access to can inundate us and overwhelm us. If we use our filters to the upmost, we can surgically select words to specify the answers we want. The quality of the clinical questions we ask determines the quality of the answers we receive when we search online databases. Just as the questions we ask ourselves daily can change our mood for the better or worse, the excellent questions we ask data bases like Pub Med can provide us with the excellent answers. An N of one study is the next best level of medical evidence. The next level of evidence is randomized clinical trial studies or RCTs used to obtain FDA approvals which are a high level of evidence and 2 positive RCTs determine an FDA indication. A meta-analysis or a review of an accumulation of clinical studies is another level of evidence. Case reports are another level of evidence. What really determines what treatment a psychiatrist recommends is his or her own experience with a particular presentation of symptoms and their response to a particular medication. We may go to a lecture, a meeting or a journal club and eventually, the conversation between physicians inevitably turns to, “what has been your experience with a particular drug.” Or what do you do when a certain drug does not work? You
may read something in a journal and try something once and if it did not work you will understand that that was not a good idea and would not do it again. If something works in a clinician’s practice they continue to do it. We are always being challenged more and more to ask better questions to help patients. Will a switch of antipsychotics help? Is augmenting a good option? Which outcome do you want to improve symptoms or functioning? Which medications do I reduce in a person who is on 9 different medications? Which medication is responsible for which symptoms? How do I determine how much to reduce which medication and how do I know if I am doing it safely enough or slowly enough? Which medications should I reduce slowly and which ones can be reduced more rapidly? How do I switch atypical antipsychotics safely while avoiding rebound or withdrawal symptoms? How do I switch people safely to Abilify, Saphris, Geodon, and Latuda when they have gained weight on Zyprexa and Seroquel? Which medications can improve dorsolateral prefrontal cortex functioning without causing mood cycling? How do I use Lithium safely? How do I manage bipolar depression safely using the rating scale? How do I use Lyrica and Neurontin in place of benzodiazepines to treat akathisia? How do I adjust medication doses of atypical antipsychotic in people with head injuries and who are medication naive? To understand how to tackle these questions first requires that a standard baseline assessment is obtained. Quantifying the extent to which symptoms are present on a rating scale and the degree to which they interfere with functioning can guide a provider to using appropriate doses of medications to treat bipolar depression.

The CMRS and tracking symptoms
The COLORADO Mood Rating scale is a 60 question self reflection scale which is designed to document a need for treatment with medications, the severity and degree of symptoms and assess someone for neural circuit inefficiency. The validity of the scale increases with a comparison with an observer rated scale and the self reflect scale. A scale is important as it can help a prescriber understand what course of treatment a person may need to improve their cognitive functioning in addition to the mood improvement people desire. People often cannot verbalize what they want and need. A scale can help them better express to care givers information that can be used to guide medication management to improve cognitive functioning. While not all people can have a dramatically improved course of illness with medications, some of the population are outliers and have excellent outcomes as a result of medication management and this as physicians is what helps us in our practices. There is general agreement among neuroscientists that in order to develop an expertise in any field of endeavor including cognitive development that about 10,000 hours of training is necessary for improvement to occur by altering brain plasticity and this applies to self awareness. 10 years of meditation practice allows people to be experts at mindfulness training, however, some improvement in the traits of kindness happiness and compassion can be seen much sooner. By spending time in thought every day, thinking about thinking, cognitive improvement occurs through mastery. Asking ourselves questions specifically about our thinking may also be thought of as a process to develop self awareness. The CMRS is a composite of several neuro cognitive assessment scales. The scale raises the bar on cognitive functioning so that improvement in executive function or planning is the ultimate goal once the other cognitive challenges are improved. The CMRS is reviewed systematically and does not replace the clinical interview. Rating scales can save a physician time by directing questions more specifically and precisely. After using the rating scale for a while, patterns can be seen immediately which are amenable to certain types of drug treatment. Problems in functioning document a need for medication treatment after a full medical evaluation has occurred. Problems in functioning that are occurring 10% of the time may not need medication treatment. Functioning problems keeping someone from going to school occurring
almost always about 90% is in need of medication treatment. MEDIAL frontal circuits dysfunction commonly causes problems with functioning at home in relationships and at work. Dorso lateral prefrontal circuits assess focus and attention challenges are easily treated and are commonly co-morbid with mood swings. Many people who are using coffee and energy drinks to excess can benefit from ADHD treatment and the result is a reduction in use of these beverages and less hypothalamic-pituitary-adrenal axis stress on the body. Cerebellar functioning and the person’s self assessment of their executive functioning or ability to plan is done last. The cerebellar functioning sub scale can be useful clinically when a dose reduction of mood stabilizers is required or a switch from one atypical to another atypical antipsychotic is required.

By reviewing neural circuitry in a systematic fashion, a medication treatment plan can be started and a general improvement in functioning and job performance can result. The major idea is that untoward behaviors need to be addressed first by treating orbito pathway dysfunction to make this pathway more efficient to improve its inhibitory effect on motor pathways. Getting rapid control of out of control behavior is where medication management shines and is most useful. The specific symptoms of sleep, energy, anxiety, racing thoughts and irritability need to be assessed and treated effectively. An excellent diet and exercise can help many people get back on track but the truth of the matter is not all of us can make the decision to eat a $5.00 bag of salad over a whopper or meditate instead of watching TV. Not everyone can give up their energy drinks, cigarettes and coffee without suffering withdrawal challenges, these circuits enable focused attention and concentration which are directly related to optimal work performance. Stimulants, non-stimulants and wake promoters can help people improve their focus and attention so that the need for caffeine and smoking go down. Cerebellar functioning and coordination should then be assessed and managed. Alcohol and opiate misuse may lead to challenges in the functioning of these circuits. When the orbito frontal and dorso lateral prefrontal circuits finally stabilize and are optimized, executive functioning or the ability to plan for the future can occur. Social interaction and the ability to work towards a common goal with others require all of our multiple neural networks to work both efficiently and in harmony with one another. The ability to be positive under extremes of negativity requires a consistently high level of functioning and efficiency of our neural networks. People who do not have a natural ability for social connection with people need to find out the pathways that are inhibiting them from interacting appropriately with others. Even though we learn our habits with respect to listening to others at a young age, they can always be improved upon. We can change the degree with which we listen to people if we are motivated enough, if we know how to do this, and if we have guidance. It is important to understand that insight into a lack of social listening ability be identified in someone early and that they be motivated to change. It is important to get the opinion of a trusted person who can be a nonbiased observer of your behavior and your thinking by having them review the check list you have filled out. This disconnects between our observing cortex and sub cortical structures can be addressed by multiple methods. It should first be assessed by filling out a check list and presenting it to a prescriber. Often people may not be candid if asked directly about their symptoms so the rating scale may be a way for others to have input into relating how they view you. The rating scale can also be filled out anonymously by several different people to see if there is a distinct pattern apparent which would lend more support to the rating scale’s validity. The rating scale identifies where someone may be able to get better and improve. Reviewing the rating scale daily and deciding to make improvements in a particular area of performance can promote improved results 4 months after a lifestyle and medication management change. The rating scale if reviewed daily can improve self -self reflection every day. The rating scale is used
by health professionals to monitor symptom response to medications and to promote symptom resolution.

**Basic pharmacology rating scale principles and the use of Abilify a dopamine partial agonist**

1. If a medication is noted after one time test dose to reduce acute symptoms by 50% on the rating scale, then a double dose should completely resolve symptoms, theoretically.

2. Medications noted to be at the highest relative effective dose are most likely to be the cause of side effects and should be reduced to the lowest possible effective dose using other agents if possible while maintaining overall remission of symptoms.

3. Dosing of Abilify at X mg dose will give X risk of side effects. X/4 dosing will reduce the risk of side effects by X/4.

4. Functioning is everything and is the best primary outcome of treatment, the measurement of functioning, however, is challenging. Does improvement in functioning mean an improvement in cognition or does it mean getting back to work? Does improvement mean improved self awareness or improved relationships? Improvement needs to be clarified at the onset of treatment.

5. A medication may be reduced once by 10% if it is the cause of 1 symptom, 20% if it is the cause of 2 symptoms and 30% if it is the cause of 3 symptoms. If the symptom resolves after a one time dose reduction and functioning is stable, then after a one month period of observation, a reduction can be sustained as long as the CMRS is done daily using a long t ½ medication.

6. Abilify is a long acting Dopamine partial agonist and may be able to facilitate dose reductions of mood stabilizers, lithium, benzodiazepines, stimulants, narcotics and antidepressants by its anti-anxiety and energy inducing effects over the course of several months.

7. Global challenges noted on the rating scale may be a result of people embellishing symptoms, and a lack of symptoms may be the result of a lack of self awareness skills. When integrity is not suspect, major disruptions in neural circuitry secondary to substance misuse, medical problems and finally mental illness are considered.

8. The CMRS always needs to be corroborated by having an accompanying person fill out an additional copy of the CMRS at an intake interview. This copy can also be used to better understand the relationship between the two people.

9. Almost everyone feels fatigue after sustained exercise. The CMRS question concerning fatigue induced by exercise can be used as an indicator of a person’s answers being valid or not or their ability to attend. It should be noted that strong athletes tend not to get fatigued after sustained exercise due to desensitization.

10. There are no current guidelines at this time for how long to maintain someone on an augmentative medication such as Abilify past a period of good response. Until such
guidelines or a biomarker is made available, the CMRS may be able to facilitate a gradual dose reduction by careful assessment of symptoms daily.

11. Small changes in medication dosing can have a dramatic effect in the long term. A dose reduction or increase in G-protein medications and transporter acting medications can be performed once and then symptoms are then assessed again in one month. If no symptoms return, then a sustained change is made. It can take weeks for receptors to change as a result of dopamine binding increases or decreases.

12. If possible, make one medication change at a time so if something happens you will know why it happened.

13. Abilify 10mg once may be utilized in place of injectable medications to ensure compliance given its long half life in people who misuse stimulants or are non-compliant.

14. An Abilify 10mg dose owns 80 to 90% of the dopamine receptors in the brain and has a higher affinity for D2 receptors than Risperdal or Haldol.

15. Abilify can be used to reduce prolactin levels in people who have galactorrhea on Risperdal and may be able to reduce prolactin levels in people who have prolactinomas and who suffer from mental illness.

16. The alpha 2 delta acting voltage sensitive calcium channel medications, Neurontin (gabapentin) and Lyrica (pregabalin) can be used to treat akathisia or restlessness associated with high dose Abilify until its dose can be reduced appropriately. These medications represent an alternative to propranolol or benzodiazepines for this purpose.

17. Abilify may need to be given twice daily at the initiation of treatment to reduce the likelihood of akathisia or side effects.

18. These rating scale principles are based on small numbers and may not be representative of a larger group of people. Humility is always an asset when treating psychiatric patients with a rating scale rating scale.
This self rating scale is effective in picking up inattention and is designed to be complementary to a clinical interview. It is not a substitute for a clinical interview. It is a time efficient way to illicit specific symptoms for a clinician to target additional information to ask questions. Orbito frontal circuit inefficiency secondary to even a minor head injury can cause a lot of dysfunction at home work and in relationships and needs to be addressed first in any treatment setting. If these symptoms are present in an environment where someone is not sleeping well and is in a state of excessive hyper-arousal then an emergency atypical antipsychotic medication designed to help with sleep can be used rapidly to give a prescriber time to make a more thorough assessment. Examples of medications that are currently used acutely are Seroquel, Zyprexa and Risperdal. As these medications can have long term side effects of metabolic syndrome and can cause fatigue and therefore cognitive challenges at higher doses, it is best to consider if a non-sedating newer atypical such as Abilify, Geodon, Fanapt, Latuda or Saphris can be use first. These medications can be used first line if symptom severity dictates that they should be used first. It is important to rule out delirium or a fluctuating level of consciousness that someone may have as a result of an underlying medical problem. It is important to know, however, that if someone is having orbito frontal symptoms as a result of substance use, a major tranquilizer may be able to lessen their symptoms and help get them into treatment. It is important to understand that anxiety can represent a medical emergency under some conditions and that the treatment of anxiety can save lives. As always, documentation of the risks vs. benefits and obtaining the persons consent should be placed in the chart.

The test dose and the CMRS
Sometimes in private practice, one does not know if the information which is made available is entirely accurate even with a third party observer present. In an emergency situation where someone has checked off all the symptoms on the rating scale as causing severe dysfunction in all aspects of life, a cautious approach should be taken. In the past, Haldol was given to people with profound psychological as well as physical consequences at high doses. We know today that the atypical antipsychotics have benefits in treating anxiety probably through their 5HT2A effect and 5HT1A effect in clinical studies. In a person who is simply seeking help from anxiety or mood swings acutely and it is not clear if drugs or alcohol or simply a stressful situation is to blame is occurring, a one time test dose of a medication such as Abilify at a level sufficient to provide an effect with a blocking of 80 to 90% of D2 receptors may be life saving and provide an opportunity for someone to decide if they want to continue to seek help regularly. Using Abilify which does not cause sedation or fatigue might be more preferable to using Zyprexa and Seroquel which do work through fatigue and sedation producing actions due to histaminic blockade. Starting an antidepressant in an emergency room without a clear history of longstanding unipolar depression may lead to cycling down the road and a return visit to the emergency room. I have seen many people in my practice who have been helped by a one time test dose of Abilify and subsequently have had 50% improvement in their symptoms and have opted to stay on the medication at a lower dose as they have noted continuing improvement on their rating scales. A one time test dose of Abilify with its four day half life will show improvement in symptoms for about 3 days then
symptoms will start to return. By filling out the CMRS daily the person sees for themselves that the medication had an effect and their symptoms slowly start to return. It is in this way that the person is able to gain insight into the fact that the medication has had an effect and that they may be more likely to continue with taking a medication that they know had had an effect of improving how they felt and most importantly to what degree. This knowledge is important for future treatment as people will need to know for example the effect of a particular medication has if they are to cross time zones and need to show up at a business meeting alert and awake. A higher one time test dose at home will give them an idea of their level of alertness the next day if they are to travel in the future and need to sleep outside their usual time zones. Sleeping medication like Ambien, Lunesta or Sonata are excellent sleep aids but they can cause memory challenges which may not be suitable for business travelers. The power of a test dose is enhanced by having the person fill out the rating scale at the time peak plasma concentrations of the medication occurs and relating the information via a telephone call. In this way an assessment of any side effects can be noted and the degree of improvement or non-improvement noted. Along with a test dose, I provide a person with a medication information sheet usually the product information (PI) with instructions to the accompanying person to call if any untoward reactions occur. A one time test dose of a dopamine partial agonist can help sort out if a hand tremor can be improved upon and restless legs steadied by the stabilizing qualities of the medication. A test dose is usually given at 10mg but may have to be reduced if a past history of closed head injury is obtained.

If there are no side effects at 2 hours when peak plasma levels are obtained on Zyprexa and Seroquel or Risperdal as a test dose, I find that the same dose is usually safe to continue. With Abilify however, it is important to know that with its long half life of 90 hours that steady state levels occur several weeks out and this can lead to a zombie like state which may result in non-compliance unless the dose is reduced. I typically continue someone only on 25% of the initial test dose if someone has had a 50% improvement in symptoms after a test dose. No atypical antipsychotic can be said to be weight neutral and children seem to be more susceptible to weight gain than adults using these medications making it necessary to be very vigilant with monitoring blood sugars and triglyceride levels. If there is not a 30% elevation of triglycerides in the first 6 weeks of treatment then there is less than a 12 % chance that triglycerides will elevate in the future when any atypical is started. Weight gain does not need to occur for elevations in blood sugar to occur.

Acutely depressed mixed manic symptoms can respond to a one time test dose of Abilify by improving symptoms by 50%. If it turns out that an antidepressant needs to be started as more history is obtained then a further response to an antidepressant may occur faster as Abilify as an augmenting agent continues to be present in the system.

The more you concentrate or attend to a task, the more you can create lasting changes in your brain which will hard wire the brain. If you attend and concentrate on love and caring the neurons which fire to make these feelings come alive consolidate and re-enforce themselves. The benefit of a test dose of a medication such as Abilify may be to interrupt the pattern of neuronal firing that was set in a state of anxiety, racing thoughts, irritability or panic so that a new pattern has the opportunity to develop. Ideally, if a new set of novel, alternative behaviors or set of emotions can be learned to take the place of the initial symptoms a better long term outcome may be possible. A one time test dose can be most useful for helping someone identify that improvement in a specific symptom or set of symptoms is possible. By filling out the rating scale at 2 hours, the brain will see for itself how much improvement there is after a test dose and this understanding...
can make insight and therefore compliance better. In addictive behaviors I have found in patients with cycling mood disorders, that the use of a stimulant or a wake promoter one time while engaging in a novel activity will trick the brain into associating the pleasurable effect with the activity and not necessarily the drug. I often have people take a one time dose of an agonist like Nuvigil or Provigil before starting an enjoyable activity like taking a morning walk. If done precisely, their mind will remember the feeling of saliency and perform the activity again daily without needing the drug. Tricking the brain in this way to temporally associate a pleasurable phasic of exogenous dopamine or histamine release with exercise or other activity can wire neurons to recognize a particular activity as something that should be continued to experience pleasure.

The medial frontal cortex is usually far removed from the sub cortical structures which are very sensitive to our perception of the external world. Because they are not directly linked up, we have developed an ability to separate emotions from decision making when needed. This separation of our prefrontal cortex from the underlying limbic structures also allow us to develop abstract concepts like freedom, justice and other social conceptualizations. Unfortunately, damage to this important area of the brain can cause its other functions like inhibition of other areas of the brain to suffer. Damage to the orbito frontal cortex can result in challenges with regulation of the body, listening and understanding others, balancing emotions, being flexible in responses, soothing fear in one’s self and others, being empathic, insightful, morally aware and can impair our ability to use our intuition. The symptoms that are present on the orbito frontal cortex circuit subscale may be consistent with symptoms seen in several different illnesses including but not limited to bipolar disorder, major depression and many different anxiety disorders. These symptoms can be treated with many different medications such as serotonin dopamine antagonists, and dopamine partial agonists. Antidepressants can make the specific symptom of racing thoughts worse and this specific symptom of thoughts that jump from topic to topic needs to be evaluated very carefully. Having racing thoughts can be indicative of someone who has mood swings and the treatment of this particular symptom represents a complex challenge pharmacologically. Managing someone who is experiencing racing thoughts while making sure they do not develop a low energy state in the future is something that we are not able to easily do at this time and represents a challenge. It can be done however, by careful daily assessment with a rating scale and starting medications at the lowest possible effective dose. Being able to calm the mind initially with medications can then enable a less invasive therapeutic method to be used such as cognitive behavioral therapy and mindfulness meditation to be more effective. We know from studies that various therapies have antidepressant properties in augmentation with antidepressants. These include talk therapies, omega 3 fatty acids, L-methyl folate, Abilify and aerobic exercise. If attention and concentration challenges are present in addition to a low energy state then a stimulant medication like amphetamine or methamphetamine, or non-stimulants Guanfacine ER Strattera, Nuvigil or Provigil may be used off label to improve these symptoms and can help with energy as well.

These circuits can be made inefficient by a wide variety of medical problems as well as untoward emotional states. Medical problems include strokes, traumatic brain injury, medication mismanagement, and medication toxicity. Before prescribing a medication to help improve memory, a note documenting the potential causes of memory impairment should be written. Namenda has 5HT3 and D2 antagonist action and may be helpful for stabilization of the NMDA system by this receptor’s antagonism in elderly people with Alzheimer’s dementia and can be used with Aricept. Galantamine works as an inhibitor of acetylcholine esterase and Rivastigmine works at acetyl cholinesterase and butyl cholinesterase to delay progression of Alzheimer’s disease.
disease. Children learn best when they are emotionally secure and they learn this best from parents who are attentive to their needs. When parents are attached to children the children get to explore more on their own and create an opportunity for learning for themselves. Emotional withdrawal hurts cognitive development and memory in children. Mood stability also influences memory and cognition. The emotional connection we have with early on in life with others determines our ability to learn to a great extent in the future. Kids are natural learners and problem solvers. They create challenges for themselves and they try to learn to solve problems by doing a task over and over again until they do it correctly. Memory circuits consolidate or are formed by repetition at regular intervals.

Parents can help children grow brain by helping their children be able to verbalize what they are experiencing and understand the emotions, then set limits when there is misbehavior. Limit setting on kids, and acceptance of who the child is and helping them learn problem solving can lead to better neurodevelopment in a child. There is no better toy to a child than a parent’s face and no piece of music that is as thrilling as a parent’s voice. A concerned parent who creates a child who explores the world with wonder and a belief in endless possibilities is a wonderful parent. Relationships and emotional connections are the foundations for learning and memory. If kids are in schools where they feel respected and valued they flourish because learning is very natural to the cognitive development of a child. Children have a heightened sense of dignity. They are very aware that they do not have a lot of power in the world and they feel the need for respect. When we are under stress we need to give each other respect under these stressful times. Kids can be taught to modulate their own orbito frontal and meso cortical circuits by having them place a toy on their belly and watching the toy go up and down with their breathing until they can understand how to meditate. Kids can also be taught to develop compassion circuitry by eating an overly ripe fruit very slowly and carefully. Developing early patience in children and the ability to delay an immediate reward for a larger award in the form of delayed gratification has been shown to result in higher SAT test scores. Encouraging self awareness in childhood pays off in huge ways as children can practice compassion and kindness by simply paying focused attention to their own states.

The DLPFC circuits or dorso lateral prefrontal circuits are involved with inattention and can become inefficient as a result of low dopamine levels in the frontal cortices. These symptoms improve as a result of treatment with either methylphenidate or amphetamine. Amphetamine acts as a pseudo substrate at both the bidirectional vesicular monoamine transporter VMAT and the bidirectional dopamine transporter (DAT). Methylphenidate however, binds to DAT and blocks it in a manner very similar to the way that the serotonin reuptake inhibitors bind to the serotonin transporter or SERT. This binding of methylphenidate to DAT is also very similar to the way that a norepinephrine reuptake inhibitor binds to the norepinephrine transporter NET. There are few D2 receptors in the DLPFC. There are D1 and D4 receptors in the frontal lobes. There is also very little DAT in the DLPFC so dopamine has to transfuse across nerve cells in this area of the brain. Treatment may involve dextroamphetamine, dextroamphetamine mixed salt, Lis-dexamphetamine. Medications like Strattera or atomoxetine, Concerta, Adderall, Focalin, and Vyvanse can all be used to treat these symptoms. Some people may be tolerant to one of these medications vs. another and if one class of medication does not seem to be working for them, another class of medication might. This is similar to the phenomena of an antidepressant class effect in SSRI treatment of depression or as in the treatment of seizures with anti seizure agents. Serotonin reuptake drugs can decrease dopamine release in the frontal lobes and cause inefficiency. A reduction in serotonin reuptake inhibitor level can improve these symptoms but can
lead to a low energy state in the future. Abilify may be able to modulate this dose reduction and improve efficiency in the frontal lobes by increasing dopamine release in the DLPFC. The DLPFC circuits which are involved with language can be made inefficient by many medications that act at GABA receptors, benzodiazepines and anti-seizure combinations can cause this quite frequently. Stroke and traumatic brain injuries can also cause people to have challenges with these circuits as well. Problems with hyper-arousal and any of the key symptoms such as sleep, energy, anxiety and racing thoughts can also make these circuits inefficient. If a medication is at the highest relative effective dose compared to others, then this medication may be able to be reduced if side effects are noted on the cerebellar subscales. Many medications can affect cerebellar subscale scores as can traumatic brain injury and stroke. Reductions in anti-seizure medications to treat mood disorders may be able to be made if someone is having symptoms of cerebellar toxicity. Adding on a low dose of an atypical antipsychotic medication such as Abilify or Geodon to Lithium or Depakote may enable a reduction in the mood stabilizer over time. These subscales will become more important in the future as medications that work through a glutamate system are being tested to treat mood and psychotic disorders. New dopamine partial agonists like Cariprazine may also be monitored through the use of this rating scale. Dizziness can be the result of Alpha 1 action that a number of anti-psychotics have and can be caused by Fanapt. Advising people to move very slowly can be very helpful for people with these symptoms and should lessen over time as a person can acclimate to this symptom. A decrease in the sense of smell may be secondary to closed head injury or smoking. Decreased sense of smell may also represent a bio-marker for someone who may be at risk of developing dementia. Executive functioning circuit inefficiency can be secondary to traumatic brain injury, stroke, and fibromyalgia and can be treated like DLPFC circuit inefficiency. Many people who are simply worn out and physically tired are unable to plan for the future. They simply live day to day and their lives are governed by existence only. Once the core symptoms of recovery sleep, energy, and the blessing of being free from all anxieties are realized then a plan for the future can occur. Planning requires that cognitive functioning is dialed in precisely. If the symptoms as rated on the CMRS are not in the almost never category then we cannot be sure that our plans will work out. You have to have an excellent functioning brain for two reasons. The first is to have a good placebo response. The other reason is to have is to be able to plan for the future. The CMRS rapidly allows someone to assess how frequently someone is having symptoms and it is understood that the highest frequency symptoms are the most probable cause of the dysfunction unless otherwise indicated. 

The Clinical interview
What is the primary task of the psychiatrist? We interview people to find out what makes them tick and we figure out what they want to do and help them do it. When someone walks into my outer office they see comfortable tan leather reclining chair with an ottoman on top of which is a clipboard with paper work which contains an insurance sheet a medication sheet and a rating scale of symptoms. I will usually greet them the moment they come to the office and I ask them for their insurance card. They will usually be observing me a lot more closely than I am observing them initially as I read the insurance card. From the moment I meet them my mind is at work
asking myself the 6 major questions I need to make a diagnosis in order to help this person become their best. I will try to assess their age their marital status their job or if they have a job. Did they sleep the night before? Do they have any anxieties? Are their thoughts racing and are they irritable? Are they using substances? First impressions are very important and but can be misleading. I also assess the person who accompanies them to see if this person is a reliable support or not. It usually takes 3 minutes for someone to fill out the rating scale and I make a note if it takes longer. If it takes longer than 3 minutes to fill out the CMRS usually means that their cognition is not spot on and typically needs improvement. Everyone gets weighed in my office to obtain a baseline. I review the medication list they give me, I carefully review the symptom rating scale to add to my initial impression, and then I ask them what I can do to help them. As they speak, I am assessing them for clues that they may have had a closed head injury in the past and any medical surgical or allergy problems with medications. I watch them intently and in a focused manner and I again wonder to myself if they are sleeping, if their energy is ok, is their level of anxiety too high or too low and if they appear irritable or are having racing thoughts. At sometime during the interview I will place my hands out in front of me to have them mirror the same to see if they have a hand tremor. Hand tremors speak to a state of over arousal of the norepinephrine system. There are many other factors that can cause a hand tremor and I make a note of the severity of the tremor. Tremors of the hands can help determine if someone is having toxicity from drugs and if someone is using stimulants such as drinking coffee. People who are in a highly anxious hyper alert state caused by insomnia may have a hand tremor. Most everyone will have a fine hand tremor after drinking a Starbucks Grande which contains 520 mg of caffeine. Some people will have a hand tremor after drinking a six pack of coca-cola, energy drinks and a few shots of espresso. Stabilizing neuronal membranes which are inherently delicate and adaptable is the primary task of the psychiatrist. I will typically write on a post it note a mnemonic for sleep, energy, functioning, physical anxiety, central anxiety (worrying) racing thoughts and irritability. My assessment is done in an organized manner so I do not forget to ask anything. If no mention of drugs or alcohol is made I ask people directly how did alcohol and specific drugs make them feel in high school and I note their response particularly if their eyes light up which I take as indicative of a notable experience. Eyes really are the pathway to the soul and when someone has a past notable experience with a drug it will give you a lot of insight into how their dopamine pathway is operating in different parts of the brain. I take particular care in asking about drugs and alcohol so as not to upset or alienate people. I do note, however, whether or not the quantity of drug or response to the drug can give me any clues as to whether or not their dopamine system is sensitive or insensitive to a dopamine acting medication. Being a psychopharmacologist is often akin to thinking like Sherlock Holmes in as much as we have to use powers of observation to develop a hypothesis then test the hypothesis to see if it works out or not. We anticipate the likelihood that a person may develop cardiovascular challenges in the future. We may wonder what kind of fast food does a person loves and how much coffee they drink. We can assess the later by looking for a hand tremor on examination while asking ourselves what the likelihood is that this person may have a major medical crisis like a heart attack within the next year. The bottom line is assessing what we can do to help a person function at the highest level possible, help them live a longer and more productive life while addressing their immediate concerns. The dietary recommendations are all the same for pretty much everyone such that everyone needs to stay away from fast food (except for Subway), no saturated milk fat, high fiber 50 grams a day, fruit, veggies hydration diet, no alcohol no drugs and they need to keep a list of their medications with their drivers license with them at all times. I ask everyone to eat salad, almonds and salmon and drink green tea. I also ask everyone to use a barrier method for birth control to prevent their getting or giving unwanted disease. I tell everyone that my office
hours are M-F 8:30 to 5:30 except for 3PM and Saturdays 10 to 4PM. I ask that a person be accompanied when they take a medication the first time as they may have untoward side effects and everyone gets a manufacturer's sheet which comes with any medications I dispense. I usually write down the method of payment with check number if they pay with a check. It is important to be able to trust someone who you see for a psychopharmacology evaluation. I am continually surprised at how often the word psychiatrist often conjures to lay people impressions not consistent with what psychiatrists truly are. I have to always remind myself however, that observer bias exists everywhere and is not limited. Bias really does exist as people want to see what they wish to be true. It is in this way that self rating scales have advantages and disadvantages. On the one hand, they are inexpensive and easy to score. On the other hand, people filling them out may portray themselves in a way they want to be perceived, resulting in self-report bias. For example, some people exaggerate their symptoms and mark all of the symptoms off as occurring all of the time. Others may check none of the symptoms off essentially saying I have no problems. Not all self report bias is intentional. People, especially with cycling mood disorders tend to have challenges self observing their problems and expressing how they feel. Having an objective third party fill out the scale based on self reflections can be helpful for a prescriber and the person being assessed. Observer bias however, needs also to be assessed as some key symptoms of irritability may be exaggerated. Rating scales should never be used as the sole determinant of a diagnosis and treatment course. Rating scales are simply a tool to help you ask better more formulated questions and save time. The Hamilton depression scale needs to be assessed at the time of the initial evaluation to document the degree to which someone is depressed. Someone ideally needs to be seen daily until they enter remission then they can be seen monthly. Exceptions to this are people who have multiple underlying medical conditions who may not be able to get their Hamilton depression scales below 7. In which case we do the best we can do with recommending a therapist to see the person weekly. If they are a chronic pain patient, an exercise program to desensitize them to pain can be helpful.

Polypharmacy
There can be a huge amount of synergy when medications are used in combination or as in an augmentation strategy. When medications are used together, especially when an antidepressant is used with an atypical antipsychotic, rapid resolution of symptoms may occur above that which is usually possible with using a single agent. Single agent treatment with an antidepressant for example can take weeks for improvement as receptors down regulate. Polypharmacy or the use of multiple medications at generally lower doses is practiced in the United States for efficacy. In other countries abroad, a general practice is to use higher doses of one medication. A basic pharmacologic principle is to increase a dose of a medication to promote efficacy until the response is limited by intolerability at which point a dose reduction should occur. Mood stabilizers are beneficial in that a rapid dose escalation can stabilize a mood rapidly through ion gated voltage channels. At higher doses however, side effects of the anti seizure medications can cause cognitive problems of word finding word switching and problems with balance. As someone is titrated upwards on any medication the rating scale should be followed carefully for any new cognitive or cerebellar challenges which may develop as these may be suggestive of side effects on a medication. The medication which is at the highest relative effective dose is usually the most likely to be the medication that is causing the most frequent and severe side effects and a one time dose reduction of 10 to 20 to 50 % depending on the number of side effects present can be attempted to relieve side effects. A follow up phone call the following day and filing out of the rating scale daily will quickly demonstrate if side effects resolve. If a one time dose reduction results in improvement, then a sustained decrease can be continued for a month.
while carefully watching for a return of symptoms. As a general principle, lithium should not be discontinued abruptly as suicidal thoughts have been known to recur. Lithium is a medication that seems to work directly on signal transduction pathways through a phosphatidylinositol mechanism of action and a glycogen synthase kinase 3 mechanism of action. Lithium has many neuroprotective effects documented and it is noted as being one of the two medications known to reduce suicidal thinking. Lithium can cause cognitive challenges at higher levels and it is probably preferable to use lower doses in conjunction with atypical mood stabilizers to treat mood swings. Geodon in augmentation studies was shown to be well tolerated when used in conjunction with lithium. Depakote, Tegretol Lamictal and Trileptal work through voltage sensitive sodium channels and in this way can have rapid efficacy but can also cause cognitive challenges quickly. Valproate has not shown as good efficacy in adolescents in recent studies as compared to the atypical antipsychotics and has been shown to be associated with lower IQ in the children of mothers who were on Depakote while carrying children.

The best way to assess the risks vs. benefits of attempting a medication change is to fill out a risk vs. benefits assessment sheet like the one noted below. The medications are placed in columns with the first column having the medication with the highest relative effective dose as noted in the PDR - physicians’ desk reference. If someone is having symptoms on the CMRS cerebellar functioning sub scale for example, the cause may be the medication in column one which would be at the highest relative effective dose. Having one symptom may require a 10% one time dose reduction and if an improvement is seen then a sustained dose reduction can occur. Two side effects noted on the CMRS may require a 20% dose reduction once, then a sustained reduction if improvement is seen. 3 or more side effects may require a 50% dose reduction or more. If the medication causing the side effects is an antidepressant medication, then an augmentation agent such as Abilify can be used to facilitate the dose reduction. If the medication is an anti seizure medication, another augmenting agent may be able to be used to facilitate the dose reduction. Benzodiazepines and sleeping agents causing memory or cerebellar functioning challenges can be substituted with Neurontin (gabapentin) or Lyrica (pregabalin) to reduce anxiety.
<table>
<thead>
<tr>
<th>Relative effective dose</th>
<th>Medication one</th>
<th>Medication two</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Keep dose the same</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevate dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect and symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medication management is optimized when a combination of an observer rated scale like the Hamilton Depression Scale, a third party report a self reflect scale and a clinical interview is performed. A psychiatrist evaluating a person who has mood swings can receive exceptional care using this method. We know that 70% of people with mood swings require at least 2 medications to stabilize their moods. The reason for this is that one medication can be adjusted for sleep while the other can be used as an energizing agent for motivation while avoiding antidepressants if at all possible. If someone has a history of Type one mood swings, suicidal thinking and an early onset of symptoms they may be a candidate for Lithium. If they have had a rapid cycling mood and a head injury then Lamictal and an atypical can be used. Any sedating drug can cause fatigue and can therefore be cognitively impairing. In the best of all settings, multifunction drugs like Abilify should be used first to avoid metabolic complications later on. Abilify can act to improve sleep at higher doses and act at lower doses to provide energy. There are many combinations of medications which can be used in this way. Assorted combinations of Lamictal which has antidepressant properties can usually be given in the AM to improve energy while Lithium at 600 to 900 can be given at night to help with sleep and stabilize mood. Blood levels of lithium above 1.0 are more likely to cause cognitive problems and I tend to use lower doses of lithium if possible during maintenance treatment to avoid the long term potential complications of thyroid or renal dysfunction. Lithium needs to be present in the body at a therapeutic intercellular level which may not correlate with extracellular blood levels. Abilify at low doses is usually given in the am while higher doses above 2mg are given at night. Wake promoters and stimulant medications are generally given in the AM. Antidepressants are usually not prescribed for people who have a cycling mood disorder as monotherapy as antidepressants can destabilize moods.
Chronic use of benzodiazepines is probably not in people’s best interest if they are causing memory or other cognitive functioning challenges and are better replaced with a medication that can treat anxiety without cognition challenges. Lyrica and Neurontin may be a reasonable off label substitute in most people for this purpose. Immediate release Verapamil used in the treatment of pregnancy induced hypertension has been shown to be safe and helpful in treating mood swings at higher doses through its calcium channel blocking mechanism of action.

Attention and concentration challenges as a result of dorso lateral prefrontal inefficiency may be treated with low dose Abilify which acts as a partial agonist. Abilify has a tighter binding to D2 receptors and as a result can displace Risperdal to reduce prolactin levels in children who have elevated prolactin levels caused by Risperdal. As the medications are listed in the top column, possible outcomes are noted that can result from an increase or a decrease in dose of the medication listed. It is in this way that risks vs. benefits decisions can be made with respect to lowering or raising medications doses.

Functional outcome and medication test dosing

The CMRS provides a way to measure functional outcome as incremental increases or decreases in symptoms can be seen with a specific intervention or therapy. The CMRS assumes that the symptom occurring at the highest frequency is responsible for or contributing to the challenges they are having with their functioning either at home, in relationships or at work. The scale provides a prescriber with information regarding symptom severity and frequency and documents how often the person is dysfunctional. This documents an acute need for treatment and the urgency of the situation. A higher frequency of dysfunction at work or school may require a higher risk medication intervention to enable a non-functioning person to improve acutely such as a child needing to get back to school. The scales with the most frequent symptoms are judged to be causing the dysfunction. The scale has only 60 questions and there are obviously many other reasons someone is experiencing dysfunction that may or may not be related to the questions on the scale. The scale gives a prescriber a rapid assessment of which symptoms need to be helped immediately to improve someone’s functioning which can be career and life saving.

The first two scales reflect MEDIAL frontal circuits which are closely tied to fear circuits and these emotional and worry circuits can profoundly affect people’s functioning. These circuits can be made more efficient rapidly and this can be done using an atypical antipsychotic quickly. The first two subscale questions, if elevated, can clearly influence all the other subscale symptoms especially the DLPFC subscale symptoms. The prefrontal cortex is usually responsible for understanding, decision making, memorization and inhibiting our actions. When the PFC is unable to do its job then pharmacotherapy is an option. While the atypical antipsychotics at an adequate dose can help orbito frontal cortex symptoms rapidly, one could make the argument that a benzodiazepine may be used to stop anxiety and many of the subscale symptoms will improve but not to the degree that an atypical will work and benzodiazepine medications while extremely effective, do represent an impaired memory risk however, which can occur even in young people and can be especially problematic for students and professionals who need to have a steel trap memory to help them under times of stress acutely. A court hearing or a big test therefore, is not the time to take a benzodiazepine but if someone is so upset that they cannot attend school or work and when just showing up is the order of the day, then using a benzodiazepine can be justified. Many atypical antipsychotics can be used to treat anxiety symptoms acutely at appropriate doses to rapidly promote symptom improvement without the concern that cognition may worsen. The use of atypical antipsychotics as anti-anxiety medications is off label but there
are positive studies supporting this use. A one time dose of Abilify at 10mg owns the D2 receptor which seems to be able to modulate many of the anxiety symptoms in the orbito frontal subscales for about 3 days. The dilemma occurs with continued dosing. Continuing someone on a high dose of Abilify 10mg bedtime may cause the person to develop extrapyramidal symptoms weeks out whereas a 5mg dose may not. So, it may be necessary to start high for a few days then drop low after the CMRS is stabilized. This may mean starting a test dose at 10mg once and if a 50% improvement in symptoms occurs then Abilify 2.5mg bedtime may be recommended. Obviously, acutely and floridly psychotic people may need to remain on a higher dose of Abilify at 10mg long standing. Children however may benefit from a dose reduction with the understanding that if they require more medication that they can take an additional 10mg dose for disruptive behavior and return to the lower 2.5mg dose or lower. Many antipsychotic naive children may benefit from Abilify 2mg at ¼ tablet am but may need to take it every three days to stop irritability and provide them with energy and improved attention and focus. The long half life of this medication makes this infrequent dosing possible. In this way, they maintain some blood level which can rapidly be adjusted if the need arises.

It is important to understand that other medical co morbidities need to be assessed and taken into account as they can influence dosing of atypical antipsychotics and therefore functional outcomes. A closed head injury of even a minor nature seems to make people very sensitive to the effect of an atypical antipsychotic such that a one time test dose may instill a zombie like state which can reduce worry and provide someone with a flat mood which can manifest over the course of 3 days. A one time negative test dose in this case will give an indication that the medication in the future will not be tolerated. A one time test dose should be able to provide the rest and sleep needed for brain recovery to help someone function optimally who is in crisis. A onetime test dose should be high enough to promote an effect change on the rating scale of at least 20%. Ideally the dose should not be so high as to cause side effects of nausea and headache. Once a one time test dose is given, a more thorough assessment may be made and if needed, an antidepressant may be used in place of Abilify. It is useful to understand that a one time Abilify test dose will be in a person’s body for several weeks and can act as an augmenting agent if an antidepressant is started to permit an even more rapid and vibrant response to remission. In my experience, the symptoms on the rating scale subside for about 3 days after a one time test dose which is about the time for 50% of the medication to leave the body. If the person feels that the medication was helpful, then a 25% daily continuing dose may be initiated to avoid a potential zombie like state which may occur in 4 to 6 weeks as the medicine approaches steady state. The improvement in symptoms is tracked such that a 50% improvement in symptoms at a certain dose may be indicative of a 100% improvement in symptoms if the dose is doubled. Of course doubling a dose brings with it the added headache of someone potentially having side effects such as headaches and nausea. The art of dosing an atypical antipsychotic medication such as Abilify requires careful consideration of someone’s level of arousal, head injury status, how well they are able to use their liver to metabolism the medication, their body mass index and medical comorbidities. If someone did have an untoward reaction to the one time test dose of Abilify, and if unipolar depression is thought to be the correct diagnosis then an SSRI can be started and the person typically has a more rapid response to it as the single dose of Abilify is in the person’s system for weeks augmenting the SSRI. In this way a test dose of Abilify 10mg may be a diagnostic marker to distinguish unipolar from bipolar depression. There are many other factors to consider, however, in determining if someone is suffering from a unipolar or bipolar depression but response to a test dose of Abilify at 10mg provides a great deal of information if symptoms are monitored by a rating scale such as the CMRS.
The memory scale at the bottom of the first page can be influenced by alterations in many of the core symptoms of sleep, energy, anxiety and racing thoughts as well as irritability all of which affect functional outcome. Dementia medications work only for about 6 months to help prevent a rapid decline in cognitive functioning as a result of Alzheimer’s dementia making the need for better medications evident. Galantamine works through an acetylcholinesterase inhibitor mechanism of action. Rivastigmine works through both an acetyl cholinesterase and butyl cholinesterase mechanism of action which is helpful in later stages of the illness. Preventing the onset of Alzheimer’s has been shown to occur through the use of cognitive training such as doing crossword puzzles and other cognitively challenging activities. New learning challenges the brain to form new connections. New activity learning and aerobic exercise are probably the best activities at this time to prevent the onset of Alzheimer’s. People who have learned a second language as children seem to be protected to some degree from developing Alzheimer’s. The only reliable way we know of to grow our memory center in the brain at this time is through aerobic exercise 3 times a week for 45 minutes. Memory is influenced by comorbid medical conditions such as diabetes, hypertension, alcohol misuse and asthma. Memory challenges may be influenced to a large degree by diet. Foods that stress our systems and especially increase cortisol release such as coffee can cause hippocampal atrophy if chronically high cortisol production occurs. It may be that starting to drink green tea and eating more fish may help reduce inflammation. Antioxidants to control the production of free radicals causing premature aging are theoretically a good idea. So far we do not have data to support that you can get high enough levels of antioxidants into the brain across the blood brain barrier to help preserve brain function. Namenda is neuroprotective and works through an NMDA receptor mechanism of action but also has 5HT 3 and dopamine action. Aricept is an acetyl cholinesterase inhibitor and can be and is used with Namenda commonly.

If the subscale symptoms on the first page are checked off as being in the almost never category and most of the challenges appear to be on the subscale symptoms on the second page, then an assessment of dopamine level or level of arousal in general needs to be made. Elevated DLPFC circuits may be indicative of a need for a stimulant medication but not always. It is important to remember that mood stability always needs to occur before cognitive functioning is addressed especially when we are supposed to keep people at work and in relationships. Once mood stability is accomplished, then cognitive functioning in terms of attention and concentration can be improved upon. Since stimulants are a controlled substance and misuse can be a challenge, most prescribers feel that people need to earn their stimulants by being consistent with compliance and using a long acting preparation first before trying a short acting medication. The decision to use methylphenidate vs. amphetamine vs. Strattera vs. Guanfacine ER is an important decision to make and assessing the risks vs. benefits is not easy to do. The decision of which medication to use is dependent on symptom severity, co morbid medical complications, past adherence issues and anticipating what someone wants to accomplish in the future and if this medication will be needed or necessary for the long term. An occasional dose of Abilify prior to stimulant treatment may stabilize mood and sleep while at the same time help anxiety symptoms. The only way to know if mood stability is occurring is to enlist the help of people who the person trusts to fill out a CMRS on their behalf based on the person’s self rating and, in this way, a third party opinion is obtained.

A history of a head injury in a person who has a low energy state may be best treated by using an anti seizure medication with energizing properties as a first line agent and this can be evaluated.
by reviewing CEREBELLAR symptoms on the third page. Someone who has had a past seizure history or even a closed head injury is subject to possibly having gliosis and subclinical seizures. If on the cerebellar subscales we see elevation on these scales, these people may be suffering from an underlying neurologic condition or are simply more sensitive to stimuli in their environment. Sensitivity to bright lights and loud noises speaks toward potential challenges with thalamic filtering as excessive sensory overload can overwhelm both cortical and sub cortical systems. Excessive cortical and sub cortical stimulation can result in a disrupted hypothalamic pituitary axis and high levels of stress hormone may result. We can see this pattern of heightened sensitivity in high energy mixed emotional states and this can be precipitated by the use of antidepressants in people with cycling mood illness. Lamictal is a very effective drug which is used in maintenance of Bipolar 1 people. It is important to remember that 1 in 11,000 can develop a potentially life threatening rash called Steven Johnson's syndrome (SJS). One SJS in 11,000 may not sound like a high number but if you understand that car accidents happen in one in 7,000 close to home you know that a rash can happen. The challenge with use of Lamictal in the long term is that a future rash that may develop precipitated by shingles or other viral illness complicating someone’s presentation requiring them to start another type of mood stabilizer while under duress. Depakote has in the past been a mainstay of treatment for kids for years. There are new concerns about Depakote as in uteri exposure to Depakote can reduce IQ points in children exposed to Depakote in uteri. If Depakote is used in conjunction with another anti seizure like Lamictal, there is an increased risk of cognitive challenges which can be detected by the CMRS as word finding and word switching challenges can become evident. Dose reduction in Bipolar disorder is performed on the highest relative dose anti seizure agent done by 10 to 20 % first then if there is an indication that the medication is causing side effects the reduction can be made on a sustained basis for a month allowing receptors and ion channels to regulate themselves. The filtering of sensory information may be facilitated by the GABA action of Zyprexa which works very well to treat treatment resistant depression (TRD) with Prozac and treats bipolar 2 as well as maintenance for acute bipolar manic and mixed episodes with and without psychosis. Abilify has the ability to also improve thalamic filter function by working through a 5HT1A mechanism of action as a partial agonist to help GABA neurons improve their functioning. Buspar is an antidepressant medication that works through a 5HT 1A partial agonist mechanism of action and can be used as an anxiolytic as well. The Veterans administration recommends methylphenidate to treat traumatic brain injury inattention and focus challenges.

Using the CMRS to aid in depression atypical antipsychotic augmentation treatment strategies
The CMRS can help people who have not yet entered remission after being treated with an initial antidepressant trial. While the current APA guidelines are now very helpful in as much as they recommend with a level 2 level of confidence, augmentation with antipsychotic medications. The recommendations do not advise us as to how long to maintain a person on an atypical antipsychotic plus an antidepressant past a period of acute response. It may be that with initiating an exercise program, and mindfulness training that these therapies may enable someone to be able to reduce their dose of atypical or the original antidepressant once in remission but this is awaiting further study. Therapy is still recommended with a higher level 1 level of consensus confidence in the treatment of major depression. Therapy is still off label but universally accepted. The CMRS is a tool that helps a prescriber review multiple symptoms, possible side effects and determine a treatment plan in one validated clinical self rating scale.
Bipolar disorder in family practice

Bipolar II disorder is an illness that occurs in 20 to 30% of people treated with antidepressants in outpatient family practices. The rate of people who have bipolar one disorder is 1.0%. Bipolar two is 1.1% and Bipolar spectrum disorder is 2.2%. These people may develop cycling moods as a result of episodic surges of BDNF and resulting synaptogenesis induced by antidepressants. This is unproven however. Bipolar type 2 people are subject to the same mood deregulation that type one people have namely they do not tolerate substances of abuse, travel across time zones, circadian rhythm disruptions, steroid hormones, or variations in diet and exercise as well. The first step in treating these people is the starting of a mood stabilizer or atypical antipsychotic medication at the lowest possible effective dose and following symptoms closely with a self report scale and third party observer to monitor response. Seroquel is approved for the treatment of bipolar depression. Zyprexa and Prozac in combination are also FDA approved for the treatment of bipolar depression. Seroquel is not approved for major depression and generalized anxiety disorder, however, it has been shown to be effective in clinical trials. Seroquel is not FDA approved for major depression and GAD but is effective for symptoms in these disorders in studies. This is important to know as many people in an emergency situation need a medication that will reliably treat a depression quickly and Seroquel for many may fill the ticket. In studies, Seroquel showed improvement in depressive symptoms as soon as in one week making it a very useful and reliable medication. Our current recommendation for the treatment for depression of a single antidepressant trial for 4 to 6 weeks is inadequate to treat many of the acutely suicidal and depressed individuals seen in clinical practice today. Many clinicians are providing excellent medical and psychiatric care by intervening sooner in an antidepressant trial and are looking at augmenting an antidepressant at 2 weeks if someone is not responding as desired. Seroquel is a very large molecule with a 7 hour half life that comes in two forms, an immediate release form and an XR or extended release form. The XR form is FDA approved as monotherapy for bipolar depression making it a very valuable medication in acutely depressed people who have mood swings or a history complicated by substance abuse of all sorts. Most experts agree that a dose of Seroquel XR at 300mg bedtime should work for most people and provide them with the 8 hours of uninterrupted sleep they need nightly. Seroquel is one of the few atypical antipsychotics that work through a NRI or norepinephrine reuptake blockade mechanism of action at higher levels which probably accounts for its FDA approvals for various depressive conditions. While it is possible to rapidly stop most antidepressants with starting Seroquel in someone presenting with bipolar depression, it is better if a bipolar person is placed on 2 mood stabilizers, first one mood stabilizer should be able to promote energy and the second should be able to induce sleep. The two antidepressants which need to be tapered are Effexor and Paxil because of discontinuation syndrome. Many mood stabilizer combinations provide energy through energy and sleep balance combination. More and more commonly Lamictal plus a sedating atypical antipsychotic is used. If Seroquel at a dose of 300mg is not working as monotherapy the dose may need to be reduced downwards however, the norepinephrine effect may be lost at doses below 300mg and an augmenting agent may need to be added. Although the signal for weight gain is less than with Zyprexa, people placed on Seroquel can have rapid weight gain which they should be made aware of at the start of treatment least they become angry. In an acute situation Seroquel has clearly saved the lives of many people. In the long term however, some people with schizophrenia and bipolar disorder have a predisposition to developing metabolic syndrome and Seroquel as well as Zyprexa can speed them down the road to cardio vascular illness. The difference between the XR form of the drug and the IR form of the drug is simply the delivery system. The same amount of drug is dispensed in say a 150mg dose of XR or IR Seroquel but the XR delivers the dose over 21 hours and the IR delivers the dose over 7 hours and therefore...
we see more of a peak blood level spike with the IR preparation. In general, people who like to sleep hard at night like the IR preparation and people who don’t like to be knocked out like the XR preparation. Higher functioning people tend to like the XR preparation better. I am not aware of any people who have developed tardive dyskinesia on Seroquel IR or XR, however, a warning for this exists as a class effect. It is important to know that the risks of tardive dyskinesia rates in the atypical antipsychotics are unknown at this time but that Clozaril is the medication that is the go to drug if someone develops a progressive case of tardive dyskinesia which does not remit after a slow taper over the course of 6 months. If someone develops cognitive challenges on high doses of Seroquel it is probably as a result of the fatiguing quality or sleep inducing quality that make it effective in bringing down depression scores in clinical testing. Recovery sleep is a beautiful thing when people are depressed however it can come at a price. The price may be seen in elevations on the dorso lateral prefrontal cortex subscale. A switch to a less sedating agent or one that has less cholinergic/muscarinic or histaminic action may need to be done if someone develops cognitive challenges on Seroquel. Seroquel has been noted to be abused by some people with addictive tendencies but in a study researchers found that the major reasons why people abused Seroquel was that Seroquel caused them to feel calm relaxed and happy.

The ideal patient for Seroquel is not the person who is already sleeping 16 hours a day and is overweight. Seroquel can be used safely in an emergency situation when the risks vs. benefits assessment weighs toward rapid stabilization of sleep to promote remission in one week at doses between 150mg and 300mg daily though higher doses may be tolerated by people who have exceptionally fine functioning livers. There is a higher incidence of diabetes in both schizophrenic people and people who have bipolar disorder and this needs to be taken into account when Seroquel is prescribed.

**Lithium**
Lithium has been around for 15 billion years. Lithium is a one plus charged molecule. Hydrogen is above it and sodium is below it on the periodic table of the elements. Lithium is of a smaller size but of similar charge compared to other major ions that we have in our brains. Lithium is an ion that stabilizes and modulates neuro-conduction and works through numerous mechanisms of action to be neuroprotective. About 100 years ago, lithium travelled across the United States in bottles as a liquid preparation and was used by the pioneers who crossed the country in covered wagons taking sips from time to time to help the pioneers relax on their long voyage. The problem was that lithium caused many of them to die from lithium toxicity if the bottle was not shaken. This heavy metal liquid preparation would often fall out of solution resulting in a highly concentrated supersaturated solution of Lithium salts in a layer at the bottom of the bottle and could produce nausea, vomiting, diarrhea and cerebellar dysfunction. If used long term, lithium taken in a highly concentrated solution could cause kidney fibrosis and ultimately kidney failure. Lithium is a miraculous substance for the treatment of type 1 bipolar disorder however. Lithium has maintained many people for years without hospitalization with type one mood swings without side effects when dosed at the lowest possible effective dose. It is also one of the only two drugs FDA approved to reduce suicidal thinking; Clozaril is the other. This alone makes the medication an amazing tool. It is thought by many that Lithium does not work below the usual therapeutic range to prevent a classic manic episode but in my practice with a type 1 mood disordered population I have treated many people who have been intolerant of higher doses of Lithium. Many people take 300mg once a day but many others take 1/2 tablets or even 1/4 tablet when combined with an atypical antipsychotic like Abilify or Geodon. In this way they are able to get the beneficial effect of lithium at a low dose which is available inside the cell or intracellularly where it is...
probably working to improve neuronal transduction. As lithium is neuroprotective, it can be acutely increased to promote sleep when needed. Lithium can also be used in people who have had their sodium levels drop on anti seizure medications like Tegretol, Trileptal, and Oxcarbamazepine. When being prescribed Lithium, it is very important to keep salt and water balance the same meaning that drinking a consistent amount of water daily will prevent side effects which can happen if someone gets dehydrated. You can think of it this way, if you become dehydrated by 10% your lithium level will increase by 10% and you could develop headache nausea and hand tremor with this higher level. Similarly, eating many bags of potatoes chips at once can reduce your lithium level by the sodium ion being preferentially taken up by the kidneys at the expense of lithium. Many people with Bipolar type one who have gambling urges sometimes find that Lithium works amazingly well to stop people from going up the hill to lose lots of money to casinos. Children who have relatives, who have been treated successfully with lithium, may find they have 3 generations of mood disorders in their family and an associated colorful family history. If they do and they themselves have an early pre pubertal history of depression, they may do very well with lithium monotherapy. Lithium tends to be weight neutral in many people which may or may not be the case with taking the atypical antipsychotics. The biggest problem with taking this very inexpensive medication is that it can be irritating when taken on an empty stomach. If you have ever swallowed a large gulp of ocean water you will have a good understanding of just how nauseated lithium can make someone if taken on an empty stomach. Thankfully, there are extended release preparations of lithium which dissolve in the lower intestines where there are no pain receptors making an extended release preparation better for many people. The real problem with lithium is that it cannot be stopped abruptly. People need to be warned that Lithium should be slowly tapered prior to discontinuation and this should be documented in the chart. A low intracellular dose level may continue in the nerve cells for a while but may leave abruptly and precipitate an acute low energy state.

People taking Lithium should perform a neuro cognitive screen like the CMRS daily to see if they are having any memory, attention, concentration or language challenges. Levels at 1.0 or lower can cause cognitive challenges and a better mood with improved energy can often be had by using Abilify at a low dose in conjunction with Lithium to lower a lithium dose to reduce cognitive challenges.

Lithium is an excellent mood stabilizer but it can cause renal failure and hypothyroidism at higher doses. We do not know exactly how lithium works but we do know that it does do a lot to the physiology to the brain acting directly on the signal transduction pathways and its mood stabilizing effect probably occurs through its effect on dampening phosphotidial inositol turnover. It also appears to work through a glycogen synthase kinase3 mechanism of action as well as increasing the anti-apoptotic protein bcl-2. Lithium toxicity can occur as it is a very small positively charged ion that looks like sodium and as such can be taken up by kidneys and retained. When this happens people can retain a lot of fluid and can swell up. At higher doses people can develop hand tremors and balance problems. They manifest word finding and word switching problems which are evident on the CMRS language and communication circuits. It is difficult to study an ion as small as Lithium to understand its exact biochemical actions but like the antidepressants and the atypical antipsychotics, it can increase BDNF and therefore can theoretically grow brain

How to use Abilify and Geodon in diabetic patients in augmentation with antidepressants
It took about 4 months for stabilization of the hypothalamic-pituitary-adrenal axis (HPAA) using Abilify and Geodon augmentation of antidepressants as noted in my patients with DM who have
had elevations in blood sugar as a result of acute depression. Their doses of atypical antipsychotics were able to be reduced once they were re-stabilized. Sugars that were running about 120 to 140 at the onset of treatment may be reduced to 110. Blood sugar is an imprecise measurement of hormonal stress levels and cortisol levels in type one diabetic people. However, when normalized in a brittle diabetic person, fasting blood sugars do represent an overall improvement in stress levels. Using blood sugar as a guide, I was able to judiciously treat patients with Geodon and Abilify off label to help treat brittle diabetic people transiently to stabilize their low energy states and place them into remission. Using their own blood sugar measurement as a guide, it was easier to identify a particular time frame by which a reduction in Abilify and Geodon could occur. So, in some people with diabetes, improvement in the hypothalamic-pituitary-adrenal axis can be helped by using Abilify and Geodon then carefully adding a dopamine agonist or stimulant like methylphenidate to improve attention concentration and focus. This seemed to improve prefrontal cortex inhibition of the hypothalamic-pituitary-adrenal axis in these people as well. It is well known that cortisol levels elevate in the presence of caffeine and this added stress seems to increase blood sugar levels as well. Many of the diabetic people who were using caffeine were able to reduce down their use by starting a medication designed to improve mesocortical pathway efficiency. Cortisol may wind up being a biomarker in the future that can help assess response to Abilify augmentation and may help determine when and how the dose of Abilify or Geodon can be reduced after augmentation takes people into remission. Acutely having an increase in blood sugar levels in a low energy diabetic is a manifestation of hypothalamic-pituitary-adrenal axis stress which may be helped by modulation with an atypical like Abilify and Geodon temporarily in augmentation. Geodon in select populations appears to have a signal for losing weight in select people on mood stabilizers and may improve blood sugars by reducing stress in otherwise healthy diabetics. Understanding the ability to modulate the hypothalamic-pituitary-adrenal axis using psychotropics is a very key skill necessary as our population continues to become more morbidly obese and children suffer from diabetes. Hypothalamic-pituitary-adrenal axis improved efficiency can enable a physician to adjust insulin medications easier in an otherwise more brittle diabetic person. Improving DLPFC efficiency using stimulants, atomoxetine, Guanfacine ER, Provigil and Nuvigil may also help stabilize blood sugars by relieving stress on the hypothalamic-pituitary-adrenal axis as well.

Treatment resistant depression (TRD)
Treatment resistant depression results after someone has failed 2 antidepressant trials in a single consecutive episode. Researchers found early in the 1990s that when Zyprexa was added to Prozac in rat models the amount of dopamine which was released in the prefrontal cortex of the animals was quite high leading the way for the treatment of low energy treatment resistant states of depression to be treated with a combination of Zyprexa and Prozac. Psychiatrists have known for decades that the most treatment resistant cases of depression have responded to a combination of an antidepressant and an antipsychotic agent. Deep Brain Stimulation is FDA approved for treatment resistant depression and although not FDA approved electroconvulsive therapy is usually thought of as being used for TRD. Transcranial Magnetic Stimulation is not FDA approved for TRD but is indicated if someone fails a single antidepressant trial. The new indications for augmentation treatment with atypical antipsychotics are an extension of this past knowledge and have a long way to go. New treatments are on the horizon however.

Research is needed desperately as the number one reason for morbidity and mortality worldwide is depression. The primary area where these people are being seen is not psychiatry but in family practice. The use of Zyprexa and Prozac in treatment resistant depression was as a result of a...
phase four studies. When we see people who have multiple emotional symptoms we are always looking at the balance of risk vs. benefit which starts at the onset of treatment and continue to every follow-up. We make decisions to treat based on our assessment of both clinical significance or the symptoms they are having and the degree to which they are dysfunctional at work, home and in relationships. We always discuss potential side effects with the person. The target symptoms we are trying to address we are trying to balance out with side effects. For individual the balance between side effects and treatment is different based on how long someone has been ill what previous treatments they have been on worked before are these symptoms new onset or chronic. We cannot always avoid side effects. We want the balance of risks vs. benefits. It is important to avoid side effects if at all possible. We have to understand that efficacy is very important in the treatment of severely depressed people. It may be in some individuals that the potential benefit in terms of functioning outweighs the risk of side effects. We have to be aggressive when we treat major depression because we know that the longer someone is in an episode of depression the longer it takes to get them out of it. We know that the numbers of people getting well on antidepressants is not great as 1/3 get a response 1/3 get remission 1/3 no response. Response is defined as someone who becomes 50% better and remission occurs when someone is 100% better. Being completely well means treating symptoms completely. Sequential treatment alternatives to relieve depression (Star*d) used sequential treatment with antidepressants to treat depression and was the largest study ever done for any particular diagnosis. This depression study was done on outpatients in family medicine and outpatient practices. The question it was designed to answer was what should someone do when an initial treatment did not work or if a second treatment did not work. From 2003 to 2004, 4,000 people participated in the star*d. These people were depressed and were not suicidal when they entered the study. They were all taken off of their previous antidepressant and put on Celexa. About 37% went into remission when they were switched to Celexa. 63% did not achieve remission and these people were encouraged to stay in the study and go on to phase 2 then phase three. In phase 2 they were offered CBT. In phase 3 they went into other types of treatment such as lithium or thyroid supplement. The study ended for those people who achieved remission. Zyprexa is a good example of a drug which was approved for psychotic condition schizophrenia then got an indication for bipolar disorder and now has an indication for treatment resistant depression. An adequate duration of a treatment trial of depression is changing as it use to be 5 to 6 weeks 5 years ago and now it is 4 weeks. If we do not see improvement in 4 weeks at an adequate dosage then we need to look at doing something differently. It is important to understand that most of the improvement seen when an antidepressant is started occurs with in the first two weeks. More and more clinicians are intervening more rapidly in order to promote remission more quickly and using more than one medication as necessary. There are two therapies used for treatment resistant treatment depression. 1. Zyprexa and Prozac 2. Vagus Nerve Stimulation therapy. ECT is not FDA formally approved for treatment resistant depression even though most people think of ECT for Treatment resistant depression. Trans cranial stimulation is FDA approved for people who have failed one antidepressant trial at an adequate dose and duration.

A Hamilton scale of 30 means that someone is clinically severely depressed and should probably be seen or contacted daily until they are in remission if it is at all possible. Many times a complex medical problem will prevent someone from entering remission and they will have a Hamilton depression scale of > 7. The combination of Zyprexa and Prozac after 8 weeks of treatment was significantly better at improving mood compared to placebo as early as one week. The big worry with using Zyprexa is weight gain and metabolic challenges after 8 weeks, 25% developed 7% weight gain of their body weight. Somnolence caused by Zyprexa is fairly common. The
American diabetic association recommends checking weight, BP, and fasting blood sugar. Gaining weight is not the only reason for elevations in blood sugar. Blood sugar elevations can occur even in people independent of weight gain. You can see triglyceride elevations within the first 4 to 8 weeks of starting an atypical, if you don't, there is a 12% likelihood of elevations in the future. Early triglyceride elevations may point to future elevations in blood sugar. If someone is going to develop weight gain it is an early phenomenon. The people who are at risk of having challenges with weight gain are the people who have gained 4 to 5 pounds in the first 2 weeks of exposure. These people may have a craving for carbohydrates. They need to eat salad, eat no saturated dairy products, and eat fruit, veggies, and a high fiber diet the first two weeks after starting an atypical as no atypical is weight neutral.

Chapter three
The care of bipolar patients
This chapter will describe how a physician may approach a patient who possibly has a psychiatric disorder. It will explain how to decide if there is inefficiency of neuronal circuits in the brain requiring treatment, using a self report rating scale, verified by a third party and by clinical interview with a Hamilton depression scale to assess level of depression.

This section will offer discussions of the most commonly encountered psychiatrically based illnesses and for each symptom a chapter describes the relevant history and psychiatric findings-then discusses the risks vs. benefits assessment of treating each symptom using evidenced based medicine. After discussing co-morbid conditions, each chapter will suggest specific and easily implemented plans for initial treatment and management. Finally, case studies of people who have been in my practice over the years have been included to provide a flavor for the long term treatment of people with psychiatric conditions and their children over the course of decades. People with possible psychiatric conditions should be evaluated in the same systematic manner as other people are evaluated in other branches of medicine. Undeviating adherence to routine is important if omission, duplication or confusion is to be avoided. Ideally, the person is allowed to tell their story and the history should be able to be written up and handed to the person with an initial treatment plan in 60 minutes on carbon paper or a computer print out. The evaluation is given to them before they go home with the person who accompanied them to the interview with precise instructions to be followed.

To save time effort and energy, a medication reference list and a self report scale are filled out by the person and the accompanying companion for validity. The medication reference sheet provides an examiner with the information needed to be able to assess the person’s past treatment response to medications and to gain an understanding of what their course of illness has been. For example, circling more than 3 antidepressant medication trials can lead a provider to understand that none of the trials was 100% effective or that compliance was a concern. Similarly three antidepressant trials may point to someone having a cycling mood disorder requiring consideration of their possibly needing an atypical antipsychotic medication. The medical history should be particularly concerned with evaluating if a past history of closed head injury has occurred as this can affect the dose needed for an atypical antipsychotic medication or may suggest that an anti-seizure medication like Lamictal may be required if someone presents in a low energy state rather than a serotonin reuptake inhibitor. A brief series of specific standard questions is asked about regarding sleep, energy, anxiety (both central and peripheral symptoms) racing thoughts and irritability. While listening to the person’s story, the provider can assess important information related to the way in which the person relates their symptoms. Often many
of the standard questions will be answered upon review of the checklist except of the 5 core symptoms of sleep, energy, physical anxiety, worry, irritability and racing thoughts. The 60 question COLORADO Mood Rating Scale (CMRS) is designed to quickly and easily recognize neuronal circuit inefficiency in 3 major circuits. The MEDIAL frontal circuit requiring an atypical antipsychotic, the Dorso lateral prefrontal cortex requiring a stimulant, wake promoter or Guanfacine ER an alpha 2 agonist. The Cerebellar symptom circuits give a provider an idea if the person is having visual or auditory pathway inefficiency secondary to neurologic illness or mood stabilizer medications which may be at higher than necessary dosing causing side effects, or illicit drug use requiring either a dose reduction in medications or a drug and alcohol treatment program.

Psychopharmacology checklist
- Review medication sheet
- Review CMRS
- Clinical interview
- Sleep disturbance
- Energy disturbance
- Functioning
- Anxiety (physical)
- Anxiety (worrying)
- Racing thoughts
- Irritability
- Past medications
- Medical history
- History of closed head injury
- Allergies
- Neurologic evaluation
- Drugs and ETOH
- CMRS most frequent symptoms
- Hamilton depression scale
- Diagnosis

* Brief psychopharmacology checklist
  1. Sleep
  2. Energy
  3. Functioning
  4. Racing thoughts
  5. Irritability
  6. Anxiety – panic
  7. Anxiety - worry

Treatment options
- Atypical antipsychotic
- Antidepressant
- Benzodiazepine or alpha 2 delta agonist VSSC
- Mood stabilizer Lamictal or Depakote VSSC
- Aricept Namenda

The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
• Lithium
• Stimulant wake promoter Guanfacine ER Strattera
• Recommendations for treatment
• Follow up phone call 2 hours after a test dose and/or appointment

The psychiatric formulation should support the major salient symptoms of concern, an abbreviated relevant medical history and past treatment response to medications. To conclude, the physician should present a formulation that answers the four questions of psychiatry.

1. What is the degree to which this person is not functional and does this lack of functioning support the need for medication treatment
2. What is the frequency and severity of the person’s symptoms
3. What are the co-morbid medical or drug misuse challenges a person may be having
4. How often do I need to see this person to get them functioning and keep them safe.

It is still unknown if a particular illness has one, several or no underlying biological causes. It is important to understand that the skill an individual practitioner has determines the ability to customize treatment to fit individual needs and plays a large part in outcome. It may be that mental illness is too complex for large population studies to be helpful; therefore, personalized medicine has the best chance of producing lasting positive change in the health care of any one individual. Family practice physicians know that using what works to motivate people to change is the easiest way to proceed to help people. For many people, what works is what we take away in the form of over the counter remedies. Family practitioners optimize health by reviewing lab work and doing a complete physical examination. They make recommendations regarding diet and nutrition and refer to specialists when necessary. Often they are placed into a situation where they have to learn how to handle complex illnesses that they really should not be treating and an important example of this is the acutely distressed individual. There are for example many cases of very ill children who are in untenable psychosocial situations and we need to be able to put out aggression as we would a fire.

The key components to thinking like a psychopharmacologist

• Understanding that less is more or using the lowest effective dose is optimal
• We only have control of the medications and not much else in treatment so limiting the amount of medication dispensed is everything and it may be that the lowest possible effective dose concept can be helpful and to our benefit.
• Medication reference sheets provide information as to the course of illness
• A validated self rating scale can quantify a response to treatment and get people into remission
• A one time test dose can provide a provider with a lot of information and saves time by seeing if a response to treatment has occurred.
• Understanding how to reduce psychototropic medication doses safely is very important
• Using the lowest possible effective dose is an important concept as it places the burden on the patient to demonstrate the need for a medication
• Which drug to use first is dependent on symptom severity, frequency, and co-morbid medical problems like head injury.
• Psychopharmacologists get sued more for what they do with prescribing medications than what they do by not prescribing medications.
• Documentation is everything when it comes to off label use

Principles for reviewing a reference medication sheet
• True knowledge is knowing what one does not know – Confucius 2,000 BC

In adults with depression:
• In depression, the majority of improvement with antidepressants occurs within the first 2 weeks of treatment suggesting that combining medications earlier may be better than a monotherapy trial for 6 weeks
• Simplifying a complicated medication regimen may help determine whether some symptoms are side effects due to medications
• Augmentation with an atypical is expensive so make sure that this option is not the only option offered
• Non-responsiveness to antidepressants suggests mixed-state bipolar disorder rather than anxious depression
• An assessment of relapses due to non-response vs. treatment discontinuation is important to know
• Non-response to antidepressant treatment with prominent apathy suggests early dementia
• If someone’s main complaint is anxiety, it may not be best to use a NDRI or NRI, as these agents do not have good evidence of efficacy in anxiety
• Many elderly people respond well to Remeron, especially those with agitated depression with reduced appetite and weight loss.
• Sedating medications may result in falls in elderly people
• Recurrences of depression can possibly indicate disease progression as shorter and shorter periods occur between subsequent episodes, with eventually poor inter episode recovery and then ultimately treatment resistance
• People with 3 or more episodes of depression should be treated indefinitely
• Sexual dysfunction is a common cause of non-adherence
• Behavioral problems typically respond to antipsychotics especially if SSRIs fail

In OCD:
• Higher doses of SSRIs and SNRIs are usually needed to treat OCD

In prodromal children:
• Childhood onset of psychiatric symptoms can turn out to be anything in later years
• In general, the earlier onset of severe symptoms, the worse the outcome. This is especially true if poor school performance and peer interactions damage self esteem.
• Mood symptoms have a better prognosis than psychotic, negative or cognitive symptoms
• Symptoms wax and wane spontaneously in children. Improvement after starting a medication may not be a result of the medication
• A delay in psychosis may be provided by using omega 3 fatty acids

In bipolar disorder:
• Differentiating bipolar from schizoaffective from schizophrenia is a complicated thing and it is best to look at symptom resolution and functioning rather than diagnosis.
• Bipolar depression may be associated with oversleeping, over eating, co-morbid anxiety, psychomotor slowing, and mood lability
• True knowledge means having a patient’s self report rating scale validated by third parties
• Obtaining blood levels will be necessary to evaluate non-response in the future in people on Effexor, Seroquel and Zyprexa.
• Rapid switching of atypical antipsychotics is neither indicated nor advised
• Bipolar adolescents are treated first line with Abilify and/or Lithium unless an emergency situation decides otherwise
• Bipolar adults usually require two medications 70% of the time one for sleep and one for energy
• Bipolar adults can be treated first line with Lithium Valproate carbamazepine oxcarbamazepine but the newer atypical antipsychotics Abilify, Geodon, Fanapt, Latuda and Saphris affect cognition less
• Bipolar depression is usually treated with caution using dopamine agonists or wake promoters in addition to mood stabilizers
• Low dose Abilify is not an FDA approved treatment for bipolar depression
• FDA approved treatments for bipolar depression include Prozac/Zyprexa combination and Seroquel XR
• Bipolar disorder FDA approved maintenance treatments include lithium, Lamictal and Abilify
• Most experts agree that the use of antidepressant monotherapy is to be avoided in people with bipolar disorder
• Clozaril and Lithium are the only FDA approved agents available to stop suicidality
• People are ideally seen daily until they enter remission unless they have complicating medical problems which prevents HAM-D from becoming < 7

Case studies

Bipolar disorder depression cases
Bipolar disorder is arguably the hardest psychiatric disorder to identify and it is the most challenging to treat. Mood swings between motivation and apathy are notoriously hard to modulate. Stabilizing serotonin, dopamine and glutamate all have roles to play in optimizing outcome. Being able to stabilize a mood in the face of environmental influences that can cause mood cycling is a challenge especially given that evidence for many treatments showing efficacy is lacking. The evidence that is available is for Seroquel, Zydis and Lamictal. Seroquel works through a NRI mechanism of action has the challenge of causing weight gain and metabolic problems long term. There are no other medications that work similarly to Lamictal aside from Riluzole. Zyprexa and Prozac as a combination has been able to treat bipolar depression and treatment resistant depression and has associated weight gain through a 5HT2C mechanism of
action. Seroquel is indicated as monotherapy for bipolar depression. Lamictal has no weight gain associated with its use is used as maintenance for treating bipolar one.

The newer third generation atypical antipsychotic Abilify did not get FDA approval for bipolar depression but it did show some benefit compared to placebo for improvement of low energy states probably through a mild sense of restlessness or akathisia. This mechanism of action at a low dose may not be enough to fully treat an episode of depression however, the art and science of polypharmacy, therapy, diet and exercise can keep people who would otherwise suffer from low energy states productive. In children with bipolar disorder, we use the lowest effective doses to get the brain back on course developing at an appropriate level.

The ski racer*

Question: Can a young female executive with type one Bipolar disorder be managed on low dose Abilify and Lamictal? How do you reduce and stop Depakote safely in case she wants to get pregnant again.

She is a 26 year white female corporate executive who had a single manic episode during college requiring a psychiatric hospitalization. She presented with a euphoric mood at an eastern Ivy League college and was hospitalized after a spending spree and having auditory hallucinations. She went on to develop side effects to lithium and she did well on Depakote for a year and then went off medications for several months. At a new job, she developed paranoid thinking at work feeling that a general message sent to the office staff about a dress code was related directly to her. It was at this point where I had first seen her and I placed her back on Depakote with improvement and she immediately became pregnant. She had been on Depakote previously but I had neglected to give her a warning about her using a barrier method for birth control. She saw a high risk OB and she decided to have a therapeutic abortion. Lithium treatment was not tolerated shortly after the hospitalization and as she engages in competitive endurance sports, I did not recommend lithium. Profound fluid shifts can occur during competitive high altitude racing and being on lithium therapy may have made her more at risk of having kidney dysfunction. Generally speaking, the effect size of response to Depakote is not as good in children as it is in adults. The effect size treating irritability and aggression is large in treating with atypical antipsychotics. We now know that children exposed to Depakote in utero have an elevated risk of having a lower IQ. Elizabeth is one of those rare people who is able to think in her dreams and do work problem solving which is a double edge sword for her in as much as she continues to need Ambien 10mg bedtime to shut down her prefrontal cortex at night for a respite. She was tapered off of Depakote for a year then became pregnant with a child. She then had an additional child. She went back on Depakote and was stable for years on but then went through a divorce and required add on therapy with Lamictal which helped with her low energy symptoms. She developed some word switching problems as a result of her being on two anti-seizure medications which stabilized her mood and had some hair loss related to Depakote. Depakote essentially doubles Lamictal levels and any dose reduction in Depakote led to a low mood five days after even a one time dose reduction. Seroquel 25mg caused her to feel like a zombie as did Risperdal 0.5mg bedtime. Question: How do you stop Depakote and transition to Lamictal using Abilify while keeping a working corporate executive functional minimizing a risk of hospitalization? Answer: You carefully reduce the Depakote monthly by 2-5% with the target to keep Lamictal at 200mg am and use the lowest possible effective dose of Abilify to stabilize her mood.

Current medications

The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
Depakote 250mg bedtime  
Lamictal 300mg am  
Ambien 5mg bedtime

Estimated Time frame to completion 2 years 6 months. So this is how the case ran. Abilify was started at 2mg ¼ am and continued throughout transition period. Depakote dose reduction was equivalent to 2-5% per month with a monthly adjustment downwards on Lamictal to get her to 200mg every am. Depakote was switched to sprinkle caps 125mg bedtime after one year. With each dose reduction of Depakote there was an increased risk of her developing a low energy state which tended to occur about 5 days after the dose was dropped once over the course of a month then returned back to its previous dose.

A Nuvigil trial was given as a one time dose to see if it helped with her energy level and it was helpful. So she now has data points to suggest that if she were to develop a low energy state in the future, Nuvigil could then be started.

She did have a euphoric initial presentation giving her a diagnosis of Type one disorder. She probably would do well on lithium monotherapy, however, she recently started racing road bikes competitively at high altitudes making lithium therapy a concern if she were to become dehydrated. She feels that exercising daily helps improve her mood by about 10% and she misses it if she does not ride her bike. The goal at the start of treatment was to have her get completely off of Depakote so if she wanted to have another child she could do so as a growing data base of patients is showing that Abilify does not at this time show an increased risk of birth defects in newborn children exposed to Abilify in utero. She still does have to take Ambien 10mg at night to shut down her brain as she still does work in her sleep occasionally.

Current medications:  
Lamictal 200mg AM  
Abilify 2mg ¼ AM  
Ambien 10mg bedtime

If she were to stop bike racing, Lithium could be started at a low dose Li3CO3 300mg ¼ tablet bedtime. The low dose of Li2CO3 would provide her with an intracellular Lithium level which could rapidly be increased, to avert a manic episode. In all likelihood she would probably not require Ambien to sleep but clearly needs it now to facilitate recovery sleep after hard workouts on the bike. Higher doses of Lithium associated with blood levels of 1.0 do an excellent job maintaining mood stability, however, they tend to cause cognitive challenges on the CMRS manifest by word finding and word switching problems. Some people develop slowed information processing speed with taking Lithium at usually therapeutic doses. Efficacy of lithium is improved with Abilify, Saphris and Geodon augmentation. Geodon is a bit of a wild card as it requires strict adherence.

In general, it is better to use lower doses of mood stabilizer medications like the anti-seizure medications by using g-protein linked medications like Abilify, Geodon or Saphris at the lowest possible effective doses to improve the chances of improved cognitive functioning in the long term.

What I’ll do better next time
• Give product information sheet and tell people to use a barrier method for birth control
• Anticipate that ski racers probably have had minor head injuries possibly making them intolerant of atypical antipsychotics even at very low doses
• Consider using Lamictal earlier on in treatment.
• Aerobic daily exercise in people with mood disorders should be encouraged earlier on in treatment.
• Abilify pregnancy registry is growing and should be reviewed regularly
  www.womensmentalhealth.org
• Warn people about the risk of Steven Johnson's Syndrome associated with the use of Nuvigil and Provigil as they both have a sulfur moiety. The risk of rash is increased in people who are on Lamictal.
• After 12 years the case goes on.

The clothier*

Question: Can a Type one bipolar salesman be managed on a low dose of Abilify as augmentation therapy to reduce Lithium and Tegretol causing a hand tremor without depressive symptoms.

He is a 26 year old white male salesman for a Madison Avenue retailer who developed a presentation of mixed manic symptoms early on in his twenties. He has had multiple hospitalizations many for severe depressions and suicidal thinking until he became stable on lithium and Tegretol. He has always run a high triglyceride and cholesterol level and had a grandfather die of multiple cerebral strokes and Alzheimer's. Mother has a history of depression treated with Zoloft 100mg am. He functions at a high level but has occasional episodes of déjà vu experiences which seem to be ideas of reference and indicative of a low grade psychosis which concerns him.

Question:
Can low dose Abilify 2mg ¼ am stabilize a mood disorder safely in a man who has an elevated triglyceride level and reduce a profound hand tremor on Lithium 450mg bedtime Lamictal 200mg am and Tegretol 200mg 3 bedtime?

Theoretically, the anti-anxiety effect of the Abilify by a 5HT1A and 5HT 2A mechanism of action should help his hand tremor but he is at high risk of cardiac complications in the future given his high triglycerides and family history.

Current medications
Li2CO3 450mg hs
Tegretol 200mg 3 bedtime’
Lamictal 200mg every AM

Time frame to completion is 1 year 5 months to try to reduce Tegretol, Lamictal and Lithium to improve his hand tremor. So, this is how I ran the case.

Start Abilify 2mg 1/4 am once with the result of improved energy. Waited a month to see if there was any risk of cycling or activation related to the partial agonist effect of Abilify. It appears that his
“cycling slowed down a little bit”. What do you want to do now? Try to reduce Lamictal as you have data points to suggest that low dose Abilify will help with a low energy state. A one time dose reduction of Lamictal was performed down to 100mg a 50% reduction then back up to 200mg. He comes back after one month. No cycling. No depression. He is skiing a lot. Still has a hand tremor but is drinking coffee in the am to wake up. He tolerated a 50% dose reduction once so he can probably tolerate a sustained reduction in Lamictal.

Current medications
Li2CO3 450mg bedtime
Tegretol 200mg 3 bedtime
Lamictal 100mg am
Abilify 2mg ¼ month

Another Abilify 2mg 1/4 one time dose was given and was tolerated well again with improved energy for 3 days without complications or déjà vu experiences. I decided to start giving him a one time dose of Abilify 2mg ¼ every month initially to see if his triglycerides would elevate further but to see if his low grade psychotic symptoms would get worse on a dopamine partial agonist. His psychosis resolved with monthly dosing of Abilify 2mg ¼ am as a result of its long 90 hour half life. I decided to maintain him at this level of medications for the next 4 months as he entered a serious relationship and was thinking about getting married.

He was still sleeping 9 hours a night but was not motivated to exercise daily running. In order to see if I could further reduce his Lamictal I gave him a one time dose of Nuvigil 250mg ¼ am which he responded to well with increased energy. He had data points to suggest that Nuvigil could be used to treat a low energy state so I further reduced the Lamictal to 50mg every am which he tolerated quite well. His hand tremor stopped. He was also feeling more comfortable with using the Abilify as he noted it gave him some energy so I recommended he take it every am.

Current medications
Abilify 2mg ¼ am
Li2CO3 450mg bedtime
Lamictal 50mg am

The next month he was using less coffee and his hand tremor is still gone. Work is causing him stress as he is stepping up his production. He wants to take the Nuvigil and I agree. I inform him that Nuvigil and Lamictal can cause Steven Johnson’s Syndrome and it would be better if he stopped Lamictal and he agrees.

Current medications
Abilify 2mg ¼ AM
Li2CO3 450mg bedtime
Tegretol 200mg 3 bedtime
Nuvigil 250mg ¼ AM

7 months from the start he is sleeping 1 hour a night less, running several times a week and is getting married. His mood is cycling slightly but he will tolerate this so he can get by with 8 hours of sleep a night and not need to drink coffee in the am so he can get back to his college weight.
He now comes in with 5 days of depressed mood. He first tried to increase the Abilify which helped a little, then he tried to increase the Tegretol which helped a little then he increase the lithium for a few days after he realized that the last Lithium tablets he received were a different preparation.

Why did he get depressed?
1. Normal mood cycling
2. Lithium level reduced upon switch to generic preparation.
By law the generic preparations of medications can have a lower or higher circulating blood plasma level at peak and steady state concentrations compared to brand name. Although he did not have a repeat lithium level drawn to confirm this we both felt that the switch to generic was the cause of his low energy state.

What I’ll do better next time
• It is prudent to be careful with low dose Abilify for as a partial agonist it can theoretically activate people.
• Should have checked triglycerides while he was off of Niacin to see if his levels decrease on Abilify as a result of improving his hypothalamic-pituitary-adrenal axis. Will get records from his Primary care.
• Should I be more hyper-vigilant with watching his mood swings now that he is on Nuvigil?
• Bring in his new wife to meet her.
• After 16 years later the case goes on.

The business man*
He was heavy drinker now sober for decades. He had an expertise for cutting deals with a flare. I started seeing him in 1992 years after he had developed central pontine myelinolysis a neurologic condition. I started him on Depakote for bipolar one disorder at 500mg and the GABA effect well treated both his irritability and mood swings well. I saw him every three months unless he was experiencing challenges with one or more of his sons or grand children. He developed a cycling mood after receiving a steroid injection for a wrist ailment early on in treatment. He prides himself on being quite precise with respect to appointments and his finances and is quite detail oriented. He smoked for decades and his attempts at stopping were unsuccessful until he had a heart attack. The decisions we make concerning our health are difficult to make and are much easier to make when we are under duress and have few options. His repeated questions regarding his life span to me were quite matter of fact. I usually responded by subtracting a few years off of the average of his parents’ ages as a result of his smoking but deep in my heart I understood that his sheer orneriness would sustain him far longer than I could imagine. I remember his being preoccupied with his only depressive episode which occurred after his heart attack which was short lived. He was intolerant of Zyprexa and standard doses probably would have elevated his already high triglycerides causing more weight gain. Elevating his triglycerides more may push him to have another heart attack. I waited to make the decision to start Geodon as add on therapy to his Depakote to reduce his intermittent feelings of irritability. He tolerated Geodon 20mg am with Depakote 500mg bedtime quite well.

“You know”, he said, “had you emphasized that I should stop smoking, I would have.” Those words sent a chill down my side as I had now become aware that my job is not simply to educate but to motivate in any way possible my people to become self care experts. The ability to look

Page 78
The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
into someone’s future and prevent a recurrent episode of illness is a beautiful thing and something we can sometimes take for granted as physicians.

Current medications
Depakote 500mg bedtime
Geodon 20mg AM

What I’ll do better next time
• Place more emphasis on the need for smoking cessation
• Place more emphasis on the need for a better diet
• After 21 years the case goes on

Mother of two teenagers
When we first met, her hands shook like a leaf and her thoughts were racing and jumping to conclusions. She had found that using Paxil at varying doses sometimes improved her mood but sometimes it did not. She was short at 5’ 2”, was 160 pounds and had been drinking alcohol to calm herself down. She presented to me as a result of some event that happened related to her drinking and her family and I needed not to know the details. On her rating scale, it was clear that her racing thoughts and anxiety level were occurring almost always or >90% of the time, I recommended that she start Geodon to help her anxiety as it functions as a serotonin transport inhibitor at a low dose but at a high dose it can block dopamine. She was not sleeping well, she was visibly anxious and was worrying for greater than 2 hours a day. Her Hamilton depression scale was 20 so I suggested she come back the next day.

Upon returning the next day she had no hand tremor, was quite relaxed and had slept well. Paxil works through several mechanism of action but it does not work through a 5HT2C mechanism of action as Prozac does. It is easy to add Geodon to Paxil but it is quite another thing to add it to a medication that works through a 5HT2C mechanism of action like Prozac which can cause intense anxiety as Geodon also works through a 5HT2C mechanism of action. What would you like to do next?
• Continue a sustained dose of Geodon
• Reduce Paxil
• Keep her medications the same

I opted to continue Geodon 20mg every AM and try to reduce her Paxil at a later date. People who have been on an antidepressant longstanding usually need it. A reduction in Paxil can be performed once a month at 10% per month if it has been taken for a long period of time. My thinking in using Geodon at a low dose was to help improve her functioning by
• Eliminating her hand tremor by helping her anxiety.
• Seeing if Geodon could help reduce Paxil which can cause weight gain
• Reduce Paxil to the lowest possible effective dose
• Starting her on a SDA which can block dopamine at a high level and decrease irritability if needed.

She comes in after 3 month having lost 20 pounds of weight. She is no longer drinking and is eating better. She is reporting that she is “lazy” and has no motivation to walk in the AM even though she knows she should. What do you recommend to improve her lack of motivation to walk in the mornings?
1. A stimulant
2. Non-stimulant
3. Cognitive behavioral therapy
4. Coach
5. Modafanil
6. Nuvigil

I asked her to take a one time only dose of Nuvigil 250mg ¼ AM once in the AM right before her morning walk to have her brain experience the phasic rush of dopamine which it would then associate with the experience of exercise and new neural pathways would be set up to reinforce the new habit of walking in the AM.

Any stimulant could do this but I chose Nuvigil off label as she did snore at night and I wondered if she may have had sleep apnea.

What I’ll do better next time
- Bring in family members for validation of self reflect scale at onset
- Document substance abuse history better

The warehouse manager

Question: Can excessive Adderall use for a prolonged period of time cause hallucinations, psychosis and paranoia?

She is a 26 year single, unmarried, no kids, warehouse manager who used excessive amounts of amphetamine to focus on doing her bookkeeping. She is 5’2 and 140 pounds. She was adopted in Korea by a local family. She had been prescribed Adderall 20mg a day in divided doses and was taking opiates twice daily to help calm her down. The last few weeks she had been taking 90 mg of Adderall a day and wound up being hospitalized for 3 days in an agitated, irritable and paranoid state. She was given a dose of Zyprexa 5mg in the hospital and was discharged to outpatient care with me and had instructions to enter a substance abuse rehab program. Initially she presents with racing thoughts, irritability and appears quite hypomanic. Her only complaint is that she is not sleeping well but on her rating scale she is irritable and has racing thoughts. I gave her a one time dose of Abilify 10 mg and asked her to fill out the rating scale again in 2 hours and call me. She reported a 50% improvement in her symptoms and I asked her to take another 5mg dose and this helped her symptoms improve by another 50%. I saw her the next day. She is of Korean extraction and appears African American in skin color. She is calmer and reports that she gets intense flushing after drinking alcohol indicative of a probable aldehyde dehydrogenase deficiency owing to her oriental heritage. She is willing to take Abilify 2mg ¼ three time a day at the same time that she took the Adderall in the past to get her neural circuitry use to at least the presence of a partial agonist to reset her circadian rhythm. I also gave her Neurontin 100mg twice daily to replace the narcotic she was taking twice daily. She refuses to enter a drug treatment program because of the cost.

Do you
1. Refuse to treat her unless she enters a drug program?
2. Do you place her on lithium?
3. Do you continue her on Abilify and Neurontin?

I opted to continue her on the medications and she dropped out of treatment with me after I gave her a prescription for a month supply of medications.

What I will do better next time
My thoughts race and my foot shales
This is a 17 year old high school student female, started on Zoloft after she became depressed when her father left on a business trip for an extended period of time. The dose was titrated upwards with the pattern that she would get better for a week then get worse again requiring the dose to be escalated. She then became suicidal after 3 months when her dose hit 150mg am. She was hospitalized for 3 days and was referred to me. The mother who has been a patient of mine for 19 years and who adopted this girl with 3 other children says she trusts you and wants you to follow her daughter as her psychopharmacologist. The hospital wants to give her Abilify and the mother wants your opinion.
Do you
1. Refuse to see the daughter because of a conflict of interest in seeing the mother?
2. Reuse to see the daughter and refer her to a child and adolescent psychiatrist?
3. Recommend lithium treatment?
4. Recommend Seroquel?
5. Recommend Zyprexa/Prozac?
6. Recommend Latuda?
7. Recommend Saphris?

I recommended she take a one time test dose of Abilify10mg. Another option would have been to start Risperdal which is seen as having better antipsychotic properties. Child psychiatrists see Risperdal as being more reliable as an antipsychotic than Abilify because it has more sedating and fatiguing qualities. It does have the challenge of causing prolactin elevation and can cause extra pyramidal symptoms as well as increase triglyceride levels. Many child psychiatrists believe that the pharmacologic mechanisms of actions of Abilify that make it suitable for depression make it not as reliable in treating psychosis maybe as a result of increasing dopamine release at low doses. Risperdal is also more sedating and Abilify is not. Use the safest medication first, then if you need to, become more invasive. Start Abilify first and dose high initially then try to use the lowest possible effective dose. I recommended that she slowly reduce down her Zoloft the same way that she was titrated up on it and start Abilify 2mg ¼ every am. She developed head ache and nausea after taking the test dose of Abilify 10mg once and, although she felt groggy in the am, she had a good family meeting the day after when her father came back from his business trip. She is reporting that her symptoms, except for her shaking foot, completely resolved after the test dose and agrees after reviewing her checklist, that since her symptoms started coming back after 3 days she would start the Abilify at a low dose with the understanding that she could call me if she needed to increase her dose. I allowed her to dispense the Abilify in the am to herself and had the mother dispense the Zoloft.

Current medications
Zoloft 100mg am
Abilify 2mg ¼ every am

She calls two days later saying that her thoughts are racing again. She is sleeping well. Her energy is good and she is not having suicidal thoughts but she is irritable. Her foot is still shaking despite the test dose.
Do you
1. Reduce the dose of Zoloft by 50%?
2. Increase the dose of Abilify 2 ¼ once, then return to 2mg ¼ AM?
3. Stop the Zoloft?
4. Increase the dose of Abilify to 2mg once, then return to 2mg ¼ AM?

You have data points after the test dose of Abilify to suggest that a higher dose of Abilify will stop her racing thoughts. There is less data to support that the Zoloft reduction will help. I asked her to take 2mg ¼ once and call me back in 2 hours which she did and she felt better. Her foot is still shaking.

What I’ll do better next time
- Have the mother control all of the medications
- Have her start an aerobic exercise program
- Fish oil capsules
- AM sunlight
- Weekly cognitive behavioral therapy
- Consider that she may have ADHD and her shaking foot may be helped by a stimulant

The closet smoker
Question: Can you treat an adolescent for anxiety while she is actively using a cannabinoid receptor agonist?

She is an 18 year old high school student who has been feeling very anxious and nervous and who did not tell you she is smoking a cannabinoid receptor agonist. She does not have a low IQ and is very engaging. Her physical examination is normal and her lab work is also normal. She is 5’3”. She weighs 117. Her mother was a competitive runner and was treated with Buspar 15mg years ago when she was no longer able to run as a result of knee pain. The patient feels better after she exercises but is unmotivated to do so. She is tremulous and restless in my office and has a 2 + fine hand tremor bilaterally.

Do you
1. Treat her with Buspar?
2. Treat her with Abilify?
3. Get a toxicology report from her primary care physician?
4. Treat her with an SSRI?

The mother calls you and tells you her daughter is smoking cannabis.

What are the risks of smoking a cannabinoid receptor agonist?
1. Can cause paranoia in predisposed individuals
2. Can cause anxiety in predisposed individuals
3. Can cause psychosis and hallucinations in predisposed individuals
4. Can cause brain grey matter loss
5. All of the above

What I’ll do better next time
• I will try to engage the patient directly related to her substance use. She did not return my calls.
• I will engage with her therapist to help engage her in treatment.
• Schedule sooner follow up appointments.

President of a country
Hector was an adopted 13 year old from south America who was named after the president of his home country before he was adopted in the U.S. He was far below reading level for his school and Spanish was his first language. He was not very social at school and would get into repeated fights. He also had several interactions with the police. He was taking Ritalin 10mg every day but his mood was not any better and it was unclear if he had been using a cannabinoid receptor antagonist or other drugs. The only time his mother could bring him in for appointments was on Saturdays. He appeared down trodden in my office and spoke slowly and hesitantly. His Spanish was not very good although mine is not either. He was quite talented drawing and brought in several of his drawings for me to see. His self rating scale validated by his adoptive mother showed that his thoughts raced and he was quite irritable. The concern I had was that this was a kid who was being treated with stimulants and was not getting any better. He was treated with Pristiq and I gave him a one time dose of Abilify 10mg and he had improvement over the course of a week. The pattern he would get into was staying up on Sunday nights and could not get to school in a rested state and he would essentially feel miserable all week long. He got better over the summer and did not come back for any appointments.

Current medications
Concerta 27 mg am
Abilify 10mg once a week on Saturdays

He initially presented with severe irritability getting into trouble with the law and was very irritable at home. The number needed to treat for an atypical antipsychotic in autism studies shows that this group of children had an NNT of 1 to 2 to treat irritability. The long half life of Abilify enables the medication to be used like a depot injection in as much as a one time dose helped him to sleep over the weekend and go to school refreshed on Monday. The Abilify at 10mg dose owns a receptor meaning that it binds tighter than the stimulant. It appears that the stimulant can help with attention and concentration in the frontal lobes where there are D1 and D4 receptors but where there are few D 2 receptors. The blocking of D2 receptors in the meso limbic pathway stopped his irritability and helped improve his mood. Some times the only way to get a medication on board is with dosing weekly with a medication that has a 4 day half life to help with assuring compliance.

What I will do better next time
• Neuro-cognitive screen with a kid who has a primary problem with language
• Clarify his diagnosis better for the mother
• Abilify helped with his irritability and was used once a week at a tolerable dose with no side effects or complaints. I dispensed it to him weekly in my office and took the burden off of the mother
• I encouraged him to read and listen to tapes to motivate him to read
• A positive word vocabulary helped him dramatically
I drive safe

Question: Can a prodromal adolescent girl be treated with Abilify 2mg ¼ every other day

She came in with her mother who says she is irritable and the patient agrees. The patient is 17, is very shy and appears anxious. She tends to overreact to a lot that happens in her environment. She wants to be an athletic trainer. She seems on my examination to have an internuclear ophthalomplegia as her eyes do not track well following my finger on neurologic examination. I asked the mother to get an MRI of her head. I discussed the risks vs. benefits of her starting Abilify at a low dose to help with her energy and her DLPFC circuits. She noticed an improvement in her irritability, anxiety and energy on the low dose of the medication quickly. She had a hard time taking the medication and would not come in for appointments. So I mailed out prescriptions for the medications and set up monthly appointments for her. She had a hard time taking the medication but was able to identify that when she took it she was less irritable. We discussed weight gain and the long term problems that could be associated with the medication at a higher dose and that if she needed to take a higher dose she knew she could call me and we could discuss it. Adolescents with prodromal symptoms are wild cards. Many of them have an excellent long term prognosis but many do not and unless you get cognitive testing you don’t know where they are on the prognosis bell curve. Some clinicians do have an intuition about who will not have a good outcome and who will not and I expressed my concerns to her mother.

What I will do better next time
• Encourage MRI of the head
• Encourage getting neuropsychiatric testing to get a baseline.
• Encourage compliance with treatment
• Express hope and understand that prodromal kids are wild cards and anything can be present in their future.

Question: How to manage someone on multiple atypical antipsychotics

The bank teller*

She is a 55 year old married mother with schizoaffective disorder. She had previously worked in a rural Colorado town as a bank teller. She is a mother of one. She previously worked as a bank teller who presents with suspiciousness and thought blocking. She had been on antidepressants long standing but had occasional lapses of energy and her thinking would deteriorate under stress. She rode horses with her daughter and spent hours shoveling out barn stalls for exercise which kept her blood sugars under good control and her weight down. She is 5’4” and 190 she was very susceptible to foot fractures because of her weight. She had been maintained on several atypical antipsychotic medications to keep her thought process intact. She ultimately required Seroquel 100mg 3 bedtime Abilify 15mg ½ bedtime, Adderall 15 every am Geodon 60mg am and 80 mg bedtime. Effexor XR 150mg am. Learning points included switch to Geodon and the use of a stimulant to help improve cortical firing and attention. Rapid discontinuation of antidepressants was a bad idea in this woman. We know that antidepressants shine in the prevention of recurrent depression from a 1970s study of Imipramine which kept people in remission until it was discontinued and then most of them relapsed in a year. Although she is still worrying she finds that knitting helps as it probably shifts the load of neural circuits from hypothalamic worry circuits to striatal circuits. Lamictal she started early on in treatment was able to be stopped after Geodon was started.
Adderall 15mg 1 every am  
Seroquel 200mg 1 and ½ bedtime  
Geodon 60mg every am and 80mg bedtime  
Abilify 15mg ½ bedtime  
Effexor XR 150mg bedtime  

She presents now with a fractured foot and is in a boot. She has not done any exercise and is picking at her skin. Her anxiety level is very high and will continue to do so for the next month while she is in a cast. What do you want to do?  
- Reduce her Geodon?  
- Increase her Geodon?  
- Increase her Adderall?  
- Decrease her Adderall?  

Given her level of anxiety and high risk of depression since she is not as active as she has been, it was decided to increase the Geodon and incur the risk of her having worsening blood sugars. The checkbook was taken out of her name. She was encouraged to be as active as she could by using a mobile one legged walker with a safety brake.  

Here is what I did  

I increased her Geodon to 80 mg twice daily and saw her back in one month hoping that she would be able to exercise and take some of the load off of her orbito frontal circuits and shift them onto the striatum or basal ganglia circuits. She comes back one month later. Sores on her skin are starting to heal over as she is no longer skin picking as much. She is napping for longer during the day and is less hungry. She is reading for 4 hours after taking her Adderall.  

What do you do now?  
Do you  
1. Reduce the amount of Seroquel she is on  
2. Reduce the amount of Abilify she is on  
3. Reduce the Adderall  

I opted to keep her medications the same. She is at the lowest possible effective dose of the Seroquel at this time as past attempts to reduce it led to a disorganization of her thought process. She is on Abilify at this time and at this dose should be a good enough mood stabilizer. She is on Adderall which is helping her focus and read. Since she is coming out of the cast on in a month I opt to wait before I do anything hoping that she may be able to start exercising to control her anxiety and weight.  

- Discontinuation syndrome of SNRIs in some people can be very concerning  
- The NRI effect of Seroquel is very helpful in treating depression at 300mg bedtime  
- Calories in equals calories out.  
- Geodon has profound serotonin transporter effects at low doses and at high doses and can help with OCD symptoms.  
- Triple antipsychotics sometimes do have a useful place clinically  
- Stimulants do help schizophrenics with attention and concentration as well as comprehension for hours if necessary.
The rower

Question: Can a Bipolar type one elderly man be managed with very low dose Zyprexa?

John is a 65 year old married father Irish catholic who drank extensively as a young man and was in multiple altercations with others. He used exercise by rowing out doors to self treat his mood swings for years and still exercises daily. He initially was started on lithium for his bipolar one disorder and developed a hand tremor. I had concerns about his developing kidney dysfunction as a result of Lithium use in an athlete. He was started on Risperdal bedtime but developed extrapyramidal side effects and a zombie like state on a dose of 1mg. History of brain trauma secondary to multiple etiologies seems to makes people very sensitive to g-linked protein receptor antagonists which should be used at very low doses. Equivalent dosing for elders may be Risperdal 1mg bedtime and Zyprexa 5mg bedtime and Seroquel 150mg bedtime worked out to be about right. He was on Lamictal and tolerated it well however he did have some intermittent mood swings. As people get older they may develop a rash and it is often challenging to separate out a potentially life threatening rash of toxic epidermal rash early in its origin in many people. In fact he did develop a zoster rash requiring him to be taken off of Lamictal as sometimes a rash can increase the risk of SJS. The medication and has been maintained on Zyprexa 5mg ½ bedtime which has GABA action which seems to work better for him than other medications. He had experienced a Lithium tremor in the past and had Klonopin induced memory loss. Exercise does seem to help with mood swings and anxiety as it is almost impossible to worry while exercising. He developed a herpes zoster rash which was difficult to sort out from a Lamictal rash. How do you determine if a rash is secondary to Lamictal?

- Blistering rash on mucous membranes?
- Non specific fatigue associated with a rash?
- One side skin rash with blistering?.
- I don’t know, I usually refer to a dermatologist to do a biopsy?

I was not sure if he had SJS but he was given a diagnosis of Herpes Zoster by his PCP and I opted to stop the Lamictal and tried Zyprexa.2.5mg ½ odd numbered days and 1 on even numbered days.

Still having sleep wake cycle disturbances.

What do you do now?

- Saphris?
- Fanapt?
- Latuda?
- Topamax?
- Zyprexa?

Topamax is not a good mood stabilizer but will probably work for weight loss and alcohol abuse. It works as a carbonic anhydrase inhibitor and it works trough a glutamate mechanism of action.

He developed a zombie like state on Risperdal 1mg bedtime. What dose would you start him on with Zyprexa?

- Zyprexa 2.5mg ½ bedtime
- Zyprexa 5mg ½ bedtime
- Zyprexa 5mg bedtime.
He did well with Zyprexa 2.5mg ½ bedtime with good anxiolytic effect probably through a GABA mechanism of action. Seroquel at 150mg is usually equal to Risperdal 1mg bedtime which is equal to Zyprexa 5mg bedtime. How do you treat people at the lowest possible dose for the shortest duration of time at intervals of every 3 months? It may be best to consider a reduction in dose or even stopping the atypical antipsychotic in an effort to allow behavioral methods to work for the person. If the person has an underlying mood problem, then using the atypical antipsychotic at the lowest effective dose is in the person’s best interest. It is interesting that in the elderly they have a lower circulating fluid volume and tend to have rapid rises of medication blood levels but at the same time with a generally higher adipose tissue percentage they tend to take a longer time for medications to taper out of their system. Patient preference is for him to see me every two months because of money challenges. He has managed to keep his weight stable on Zyprexa and he is not angry or irritable with his wife.

What I’ll do better next time
• Get more information from son regarding benzodiazepine use
• Patterns of sleep disturbance guide medication dosing
• When to consider dementia vs. depression
• What dose of an atypical is an adequate dose in the elderly?
• Studies show Risperdal 1mg = Zyprexa 5mg = Seroquel 150mg

The sportswoman*
She is a 36 year old woman college student who developed suicidal thoughts and had killed a cat while having auditory command hallucinations. She has had homicidal thoughts longstanding helped by LiCo3 300mg 3 bedtime, Abilify 15mg ½ bedtime, Zyprexa 5mg ¼ bedtime and Nuvigil 250mg ½ am. I dispensed the lowest dose of lithium to her possible to maintain her mood but she has cognitive challenges anyway. A rating scale helps track her thinking. Lamictal helps with energy but rash problem is a problem. She is 249lbs and 5’4” tall overweight and has had multiple knee surgeries and head injuries which were sports related. She snores and her brother is on a CPAP machine. She had hemochromatosis for many years as a result of her having amenorrhea. She had an episode of a cycling mood with Wellbutrin and developed racing thoughts and voices. Attempts to reduce her Zyprexa resulted in a return of voices. She lives in a small town in Colorado and travels to Denver accompanied to see me every month. She was started on Seroquel and although was not able to lose weight her weight did remain stable for a long while. She feels better after eating salad saying she has a feeling of well being. Her leg is in a brace after developing an enlarged bone in her foot and she is more irritable. She was treated with Seroquel which treated her depression and voices and subsequently had Abilify added to enable a reduction in lithium but further reductions of lithium were of a concern for her as she would become rapidly depressed. She understands that Zyprexa helps with the voices and Abilify helps with her irritability and even a one time 25% dose reduction once caused a tendency towards irritability over the course of a month. She has no hand tremor and she is having challenges losing weight and has sleep apnea helped by Nuvigil which enables her not to nap during the day. She used exercise to stabilize her mood for many years and has had multiple knee surgeries. Abilify augmentation allowed for a 25% reduction in her lithium dose and improved her cognition.

What I’ll do better next time
• Do not be overly afraid of starting overweight people on low dose Seroquel or Zyprexa. There may be a dose response curve for weight gain on Zyprexa and you may be able to get away with using it at low doses in people who have had multiple head injuries.

• Wellbutrin can cause cycling in some people who have a cycling mood even though it binds DA receptors with 10% occupancy. Wellbutrin’s ability to cycle a mood may be secondary to the additional NE effect. It was a small case series done in the early 1990s that led people to believe that Wellbutrin did not cause cycling in bipolar people and it got into the guidelines as a drug that was less likely to cause cycling.

• Risk of cycling is highest with tricyclics then SNRIs then ssris and MAOIs may tend to cause cycling less though this is variable.

• So after 18 years the case goes on.

The artist

Question: Is it worth the effort to get a bipolar type one person back to work within one year after a psychotic break.

She is a 40 year old sales woman, a mother of 3 teenage sons, who developed paranoid thoughts and ideas of reference that her boss was hitting on her and was hospitalized in a floridly manic state placed on lithium and Zyprexa. She presented at the same age as a relative who also developed a similar mood state. She was started on Zyprexa 7.5mg bedtime and Li2CO3 300mg 2 bedtime. She developed a flattened and depressed mood afterwards and lost her creativity and drive for painting. Her husband was completely supportive of her through her ordeal. She liked working which was different for her than the difficult job of caring for her 3 teenage sons. She felt a sense of contributing to the family working outside the home and missed this aspect of working. She felt upset about how she was treated at work and was not sure that she wanted to go back to work but wanted to know that she could work again despite her illness. After a period of recovery we discussed her going back to work and she was able to do so with Lamictal 50mg am which gave her energy and was able to go back to work. She functioned well at work in a higher energy state, however, her higher energy was not welcomed in her personal life and she stopped working and returned to caring for her 3 teenage sons at home and her painting. Overall she felt better about the fact that she was able to return to a highly stressful work environment despite feeling traumatized by it. Her improved self esteem has carried her to this day as she is much more confident about her abilities in multiple aspects of her life. Her ability to have been able to provide monetarily for her family was a strong source of satisfaction for her. She maintains her creativity in painting and feels better with exercising by mowing the lawn weekly. Her small kidneys and recurrent urinary tract infections make monitoring of her lithium levels important as well as monitoring of creatinine levels. Returning to work within one year was of therapeutic importance to her. She felt that it was her decision as to whether or not she wanted to work and in what capacity. She ultimately decided it was more important for her to care for her 3 teenage boys. She was able to make the decision on her own and that was very helpful for her in the long run. She has been able to maintain her high school weight with little challenge by being on the lowest possible effective dose of Zyprexa and lithium without cognitive challenges. On both medications, her weight has been maintained mostly by eating salad daily which has also improved her cognition. By increasing biopterin to increase monoamine synthesis and by methylating her DNA reducing copies of COMT, an enzyme which metabolizes dopamine at the synapses in her prefrontal cortex, an area devoid of D2 receptors.
She has not gained weight on lithium and Zyprexa whereas her relative who was on the same combination gained a lot of weight.

Do you change her to Abilify or maintain her on Zyprexa and Lithium at a low dose which does not have a signal for weight gain? I opted to continue her on the treatment for which I had data points that suggest it works.

What I will do better next time

• Get the husband involved with a return to work plan
• Very small dose changes in g-protein linked medications can have a profound effect on mood
• Lamictal can make so people have a lot of energy and make even the nicest people irritable.
• Some genes turn on in some families and turn off in some families based on nature’s time clock which may not involve pruning but some other mechanism we do not fully understand but may in the future
• Understand that higher doses of Zyprexa can take away creativity and after an acute manic episode it may take months for people to return to normal functioning if not years.

She has gained 10 pounds of weight planning a wedding for one of her sons. She says she has not been exercising as she usually does and has been more sedentary. She also has not been eating as much salad.

Current medications
Zyprexa 2.5mg ¾ tablet bedtime on Sundays, Wednesdays and Fridays
Zyprexa 2.5mg ½ tablet bedtime on Saturdays, Mondays, Tuesdays and Thursdays
Li2CO3 300mg 2 bedtime

What do you want to do?
• Switch her to Latuda?
• Switch her to Abilify?
• Reduce the Zyprexa?
• Encourage diet and exercise after the wedding?

I opted to further reduce her Zyprexa to ¾ on Wednesdays and Fridays and ½ on Saturdays, Sundays, Mondays, Tuesdays and Thursdays.

• After 8 years, the case goes on

The great mother
Question: Should a mother with homicidal thoughts toward her first child have another second child?

She is a 34 year old married medical technician woman who presented with obsessive thoughts of harming her new born child after a 65 pound rapid weight loss following the loss of a relative. She was hospitalized because of OCD thoughts and was discharged on an SSRI. After I evaluated her...
it was apparent that she was getting worse on antidepressants and I placed her on lithium with a
good response. Her interactions with her child were always exemplary and she was indeed a
great mother and I told her so. Now on Li2CO3 300mg 2 bedtime she wanted to have a second
child. What are the psychopharmacology principles necessary to keep in mind when women want
to get pregnant?

Pharmacotherapy pregnancy recommendations

- Pharmacotherapy during pregnancy should be avoided if at all possible especially during the first trimester during fetal development
- Use the minimal effective dose of psychotropic medications during pregnancy
- Partial treatment carries the risk of both teratogenesis and maternal psychiatric decompensation
- Monotherapy is preferred during pregnancy
- Psychotherapy is a useful adjunct treatment during pregnancy
- ECT is always an option during pregnancy
- Women taking conventional antipsychotics tend to have lower birth weight infants and women taking atypical antipsychotics tend to have higher birth weight infants

While lithium should usually be discontinued during the first trimester during the period of time that
fetal cardiac development occurs, further reductions in her lithium made her develop a low energy
state and I recommended that she continue on Lithium throughout her pregnancy. Heart
malformations are now detectable with level two ultrasounds and cardiac repair procedures are
becoming routine. Her lithium which was maintained throughout the pregnancy enabled her to
care for her daughter and kept her out of the hospital. An attempt to reduce her dose of lithium
further resulted in depression and a low energy state. She maintained a Lithium Level of 0.3 to
0.4 and this was adequate enough for her to maintain a stable mood and work full time. Her
diagnosis is bipolar type one. The take home points for this case are that you don’t treat a blood
level. Even homicidal people can do well and be asymptomatic with levels in the 0.3 range. Her
homicidal thoughts were ego dystonic or upsetting for her and she was not delusional. The
precipitants to her first hospitalization were clearly related to her weight loss and a resulting
metabolic imbalance. Acute grief complicated her initial presentation. She tells me that she is
going on a cruise to the Caribbean for 1 week and wants to lose 40 pounds having bought the
P90 X work out plan.

What do you want to do?

- Tell her to enjoy herself on her cruise?
- Tell her to watch for a hand tremor which may increase by 10% with each 10% weight
  loss she accomplishes?
- Encourage her to eat fruits, veggies, salad, almonds and drink green tea?
- Encourage her to drink a post work out recovery drink of fat free chocolate milk within 30
  minutes of finishing exercise?
- Carry her medications with her at all times and spare medications in her suitcase?
• Inform her that abruptly stopping Lithium can result in suicidality and in her case homicidality?

I knew that during her pregnancy when her Lithium was reduced to 300mg 1 and ½ bedtime that she developed a low energy state which immediately improved in one day upon raising the dose to 2 bedtime.

When a mother has fear about killing her new born baby daughter, psychiatrists become involved and hospitalization occurs. Many of these women have mood swings which are easily treated with medications. Unfortunately, antidepressants make this condition worse for people with a cycling mood as it did for my patient.

Current medications
LiC03 300mg 2 bedtime

Would you consider an Abilify trial in this woman?

She should probably try the Abilify if for no other reason than to assess her response to it as her children have a 50% risk of developing bipolar disorder in the future. She refused to take Abilify. Her second child was large at birth. Many women who are on atypical antipsychotic medications have large sized newborns. Women who have had children on conventional antipsychotics have generally smaller new born children. Had she been on Abilify, her second child may have been larger.

• You need to stop Lithium during the period of cardiac formation early in the first trimester then restart it if possible
• Weight loss can precipitate a manic episode but it is difficult to know if a manic episode started before her weight loss.
• Rapid shifts in water balance and weight can precipitate a manic episode.
• Hand tremor can be used as a guide to monitor Lithium levels and can be reduced with high potassium fruits and veggies temporarily
• The post partum period is the time of highest risk for depression
• Rapid fluid shifts during delivery can cause salt and water balance fluctuations affecting lithium
• After 14 years the case goes on

The bookkeeper
Question: Is working in a high pressure job ok for a chronically psychotic individual with OCD traits?

She is a married 54 year old accounts receivable executive woman I initially saw in 1997 with paranoia and obsessive symptoms of checking and rechecking her work. She has a mood disorder with depressive and OCD features and had been on higher doses of conventional antipsychotics in the past when I initially started to treat her. She was treated with Abilify with good results. Her weight gain was due to a combination of hypothyroidism and Zyprexa at a
higher dose. Using Abilify has lead to a tapering of her Zyprexa medication over time. Her sedentary lifestyle and thyroid problems make weight loss a challenge.

Current medications:
Abilify 5 ¾ bedtimes
Pristiq 50mg bedtime
Zyprexa 5mg ½ bedtime

On these medications she is able to handle stress quite well at work. She still feels that others at work are talking about her behind her back. She has been getting bonuses at work and her job appraisals have been good. She has always been obsessed with getting things perfect at work which is probably why she still has a job.

She wants to lose weight and asks if there is anything that can be done pharmacologically to help her lose weight.
Do you
• tell her to eat more salad?
• tell her a stimulant might increase both her anxiety and paranoia?
• Decrease the dose of Zyprexa down once by 25% and return to its previous level to see if she has a change in her rating scale over the next month?
• Tell her to eat non-fat milk products?
• Tell her that a high fiber diet > 50 grams a day will require her to take a multivitamin?

Here is what I did:
I gave her a Zyprexa 2.5mg tablet and had her break it into fourths and had her take ¾ tablet once then return to Zyprexa 5mg ½ bedtime every night. She had more challenges sleeping the night of the reduction and did not function well the next day. She will fill out the rating scale over the next month to see if there are any changes and we may try another attempt at another dose reduction in a month.

She has not had mood cycling at all and is typically non reactive to stress other than she feels over whelmed and depressed at times. She is deeply religious and this seems to have helped her continue to work under periods of time of her having low energy states. She is able to stay away from sugary foods at work. She does eat fat filled cheese however. It is not clear to me if milk fat from cows mounts an inflammatory response in our fat cells in our gastro intestinal tract which stimulates an increase in fat receptors on fat cells to maximize fat absorption and calorie absorption. Every time I look at a two-year olds’ baby belly stick out, it reminds me that our abdominal fat is an organ designed to absorb massive amounts of calories and it may be that a drop of milk fat is the chemical signal for massive absorption of calories to occur. It may also be that saturated milk fat may cause an inflammatory response to facilitate this signal. Milk fat from cows has high amounts of fat in it compared with human milk. Cows milk is designed to get a calf from 60 pounds at birth to 1,000 pounds in one year. Human milk is designed to get an 8 pound infant to 150 pounds in 16 years.

What will I do better next time?
• Engage her husband in a discussion regarding her illness and treatment?
• Get a validated CMRS from the husband?
• Encourage the husband to enter a weight loss plan with the patient?
• After 14 years the case goes on

The clerk*
Question: Can Geodon be used as an anti-anxiety agent at a low dose in conjunction with Depakote to reduce an essential hand tremor better than propranolol?

He is a 65 year old married accounts manager for a telecom company who has a history of heavy drinking and type 1 mood swings who presents with a history of irritable mood, elevated triglycerides who presents with severe anxiety and profound hand tremor secondary to a combination of his resting tremor and Depakote. He has been well treated with propranolol 20mg am and the addition of Geodon 20mg AM has helped keep him stable. Geodon 20mg am and Depakote 500mg 2 bedtime. He had a gun pulled on him at the store he worked at and felt better taking lorazepam 1mg which although stopped his hand tremor it made him fuzzy and he had some mild cognitive challenges with word finding probably as a result of the combination of the two anti-seizure medications he took. He had been on Lamictal in the past which gave him energy and pulled him out of a depressed state, however, he developed an irritable mood on this medication when combined at a low dose with Depakote. He now has severe chronic back pain which has become worse over the last few months and appears anxious in my office sitting upright in a stiff manner. He says that when he walks he occasionally will experience a sharp back pain that makes him halt abruptly and stop moving. He has been sober for years and is active in AA.

Current medications
Depakote 500mg 2 bedtime  
Geodon 20mg every am  
Propranolol 20mg every am

What do you do now for this man?
• Refer him for back surgery or an evaluation?
• Consider Lyrica or Neurontin which work through voltage sensitive calcium channels to reduce pain and anxiety?
• Tell him to eat more salad to promote weight loss and improve cognitive functioning?
• Tell him that while his hand tremor was better initially on Geodon it is now worse probably because of excessive norepinephrine output secondary to pain?
• Prescribe an opiate?

Here is what I did:
I referred him for a surgical evaluation. I have data points to suggest that a benzodiazepine will help his anxiety through a GABA-A mechanism of action however, his cognitive functioning on it was poor. His excruciating level of pain might be helped by an opiate. The sedating and fatiguing properties of an opiate in combination with his other medications may cause his cognitive functioning to be further compromised. I referred him to seek a surgical opinion. Any medication that reduces arousal levels has the potential to reduce cognitive functioning especially in a man who is taking a mood stabilizer and an atypical antipsychotic.
His wife comes in with him and says he is fatigued all the time and irritable 3 months after starting Geodon.

What do you do now?

- Reduce his dose of Depakote 500mg 1 ½ bedtime
- Increase Geodon 40mg am
- Stop his propranolol
- Reduce his Depakote once to 500mg 1 ½ bedtime for one night then return to 2 bedtime.

It can take a few months for receptors to adjust to augmentation with an atypical antipsychotic even at a low dose causing sedation. Since he may be going to surgery I opted to reduce the dose on a sustained level knowing that Geodon augmentation could be used to help him at a higher dose with sedation if needed.

What I’ll do better next time:

- Have the wife validate his CMRS
- Promote more weight loss earlier with a vegetarian diet and exercise program
- After 11 years the case goes on

The writer*

Question: How do you switch from Saphris to Latuda with augmentation therapy with Lamictal and Lithium?

Questions: how long does it take for nerves to regenerate after a crush injury?

Question: How rapidly can you taper a barbiturate?

Question: Does fish oil really help?

She is a 26 year old white female with pre-pubescent onset of a mood disorder manifest by insomnia. She self treated her mood disorder as a teenager by swimming competitively and reading when she could not sleep at night. She was treated with multiple antidepressants and developed mood cycling associated with visual hallucinations seeing snakes. I initially placed her on Lithium to stabilize her mood and she overdosed on lithium requiring ventilation and was in the ICU for a week after she was found down in her home on her side and had a crush injury of her arm resulting in a left sided hand tremor. Her mood has always been regularly unstable. She has always written beautifully as an avenue for self expression. She was placed on Geodon 80mg twice daily in addition to Lithium and tegretol and managed to lose a significant amount of weight and developed serotonin syndrome. Primidone, a barbiturate, was used at a low dose to help with her hand tremor. She is 6’ 2” and weighs 200 pounds. She was treated with low dose Seroquel in the past and was hospitalized with an allergic reaction which sent her to the ICU again. She had been stabilized most recently on Saphris 5mg am and 10mg bedtime, Lamictal 200mg am, Lovaza 1gram 4 bedtime and lithium 450mg bedtime. Over the course of my treatment with her she married and adopted 4 children whom I had concerns about in terms of her, not being able to handle the stress of parenting so many children although I was certain she would be an excellent mother. I also recommended that she not get pregnant as her past history of hospitalizations lead me to be concerned about her mood stability post partum. She was able to carry the child, however, to term using a fish oil supplements off label for sleep. She developed

Page 94

The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
thyroid cancer over the course of the last year and is currently in treatment for this condition. She had felt fatigued as a result of her thyroid condition and she gained benefit from Nuvigil 250mg ¼ am but developed insomnia and it had to be stopped after one month. A one time dose of Lexapro 10mg caused her mood to cycle before the Nuvigil trial.

Current medications:
Lamictal 300mg am
Li2CO3 300mg 3 bedtime
Lovaza 1 gram 4 bedtime
Saphris 5mg am 10mg bedtime
Primidone 50mg bedtime

Now on primidone 50mg hs Lamictal 300mg bedtime saphris 5mg am and 10 mg bedtime Li2CO3 30mg 3 bedtime lovaza 1 gram 4 bedtime. She gained weight on Saphris at 210 and wanted to try a new medication which would you do first?
1. Latuda 40mg ¼ am
2. Latuda 40mg ½ am
3. Discontinue primidone first to increase her Lamictal level
4. Discontinue primidone to simplify crossover titration
5. Discontinue Saphris immediately then start Latuda at a full 40mg dose.
6. Start Fanapt at 2mg 1/2 pill once

As she had always had challenges with sleep, I decided to recommend she start Fanapt 2mg 1/2 once to help her with her sleep through an alpha 1 mini press mechanism of action. She developed a zombie like state on Fanapt and felt over sedated. I next opted to try Latuda and it was started at Latuda 40mg ¼ am as a test dose with an improvement in mood so she was started on this at a sustained dose. Primidone was discontinued to a ½ tablet for a week then discontinued. Primidone is known to induce the P 450 enzyme system and discontinuing it would increase Lamictal levels reducing her risk of developing a low energy mood state. Rapid switching of atypical antipsychotic medications is neither recommended nor advised except under conditions of hyper-osmolar coma, and neuromuscular malignant syndrome

Latuda has a signal for weight loss at low doses. She felt immediately sedated the next day and was able to stop her AM Saphris the next day. She took the Saphris 10mg bedtime and became less hungry over the next month and she lost 2 pounds.

Her rating scale shows that she is not experiencing any challenges with respect to her neural circuitry. Do you reduce her Saphris down or maintain her on her current medications?

Current medications
Saphris 10mg Bedtime
Lovaza 1gram 4 caps bedtime
Li2CO3 300mg 3 bedtime
Lamictal 200mg 1 and ½ every am
Saphris 10mg ½ bedtime

What do you want to do now?
- Keep the same dose
• Stop Saphris
• Reduce Lamictal for potential for cognitive challenges.
• Reduce Li2 CO3 because of potential for cognitive challenges.

I opted to keep her medications the same for one month to avoid the likelihood of rebound withdrawal of muscarinic and histaminic receptors and resulting insomnia which would lead to a cycling of her mood. I have found that slow plateau switch enables me to use the lowest possible dose of a new atypical antipsychotic when it is started.

She did not tell me that one of her daughters was started on Zoloft and her dose was titrated up monthly by 50mg to 150mg until she developed suicidal thinking and was hospitalized. My patient tells me that I am the only person she trusts with her daughters care.

• Do you refer the child to a colleague as it is a conflict of interest for you to treat the mother and her daughter?
• Do you see the child on a medication only basis and have the child see a therapist weekly
• Do you treat the child who is having insomnia with omega 3 fatty acids or with a mood stabilizer knowing that the mother has a cycling type one mood disorder and has done well on lithium?
• Do you start low dose Abilify 2mg every 4 days to reduce her irritability and have her find her own lowest effective dose?

I opted to see the child.

What I’ll do better next time
• Need to have lithium dispensed to a person during periods of high risk
• People who do not take their lithium and stop it abruptly may become suicidal quickly and should be warned and documented
• Mothers who have had more than 6 hospitalizations in the past may still make great mothers
• Never try to talk a woman out of having a child
• Never try to talk a woman out of adopting 4 children
• Always be available by phone or pager anywhere you go in the world
• Be careful when you prescribe Primidone for hand tremors as it decreases other drug levels by P450 interactions. Abrupt barbiturate withdrawal is one of the most lethal withdrawals we have in medicine. By binding to GABA-A receptors irreversibly barbiturates can cause sustained hyper-polarization of nerve cells. Rapid withdrawal can results in coma and death.
• After 16 years the case goes on

The teacher
Question: Can you refuse to give Ambien to a bipolar patient who babysits her daughter’s infant child at night several days a week who already has profound memory challenges?

60 year old retired teacher with breast cancer and several previous episode of auditory hallucinations associated with depression has a diagnosis of bipolar one disorder, cognitive impairment, past ECT treatment and past klonopin use associated with memory loss. My first
evaluation of her occurred 1998. She was intolerant of lithium by her report. She received chemotherapy for her breast cancer. She manifests some mild executive dysfunction and verbal memory problems. Antidepressants precipitated psychosis in this woman in the past on several occasions.

Current medications
Trileptal 300mg 2 bedtime

She developed profound tremors on Geodon and Loxitane made her flat and depressed. She was intolerant of the atypical antipsychotics at standard doses. She was demanding of Ambien and she left my practice. She left my practice before the newer atypical antipsychotics came out. Many of the newer atypical antipsychotics act as antidepressants to treat lower energy states well.

What I’ll do better next time
• Consider another preparation of lithium at a low dose
• Consider Latuda
• Consider Saphris
• Consider low dose Abilify
• Consider Agomelatine an M1 M2 agonist and 5HT 2C antagonist.
• Consider Selegiline – an maoi
• Cognitive behavioral therapy

<table>
<thead>
<tr>
<th>Half lives of selected atypical antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saphris</td>
</tr>
<tr>
<td>Abilify</td>
</tr>
<tr>
<td>Clozaril</td>
</tr>
<tr>
<td>Haldol</td>
</tr>
<tr>
<td>Latuda</td>
</tr>
<tr>
<td>Zyprexa</td>
</tr>
<tr>
<td>Invega</td>
</tr>
<tr>
<td>Trilafon</td>
</tr>
<tr>
<td>Seroquel</td>
</tr>
<tr>
<td>Risperdal</td>
</tr>
<tr>
<td>Geodon</td>
</tr>
</tbody>
</table>
Atypical Antipsychotic Switching Principles

- Maintain receptor blockade at current level by carefully assessing dosing of the current agent
- Rapid switching is neither recommended nor advised
- Rapid discontinuation of an agent with high H1, M1 or M2,4 blockade can cause rebound or withdrawal anxiety, agitation or diarrhea
- Rapid discontinuation of an agent with high 5HT2A blockade can cause rebound or withdrawal EPS/akathisia and possibly psychosis
- Rapid discontinuation of an agent which has high D2 blockade can cause rebound or withdrawal psychosis, mania, agitation, or withdrawal dyskinesia

Antidepressant use in bipolar depression

<table>
<thead>
<tr>
<th>Favors antidepressant use</th>
<th>Discourages antidepressant use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar two</td>
<td>bipolar one</td>
</tr>
<tr>
<td>Depressed non mixed states</td>
<td>mixed manic and depressive states</td>
</tr>
<tr>
<td>Absence of rapid cycling</td>
<td>presence of rapid cycling</td>
</tr>
<tr>
<td>Absence of recent mania or hypomania</td>
<td>presence of mania or hypomania in past</td>
</tr>
<tr>
<td>In past 2 to 3 months</td>
<td>2 to 3 months</td>
</tr>
<tr>
<td>Absence of drugs or substance use</td>
<td>presence of alcohol or substance use</td>
</tr>
<tr>
<td>Prior favorable response to antidepressants</td>
<td>poor response to antidepressants</td>
</tr>
<tr>
<td>No history of antidepressant induced mania</td>
<td>presence of antidepressant induced mania /hypomania</td>
</tr>
</tbody>
</table>

How rapidly can you stop an antidepressant in a bipolar person?

The principles behind stopping an antidepressant in a bipolar person are straight forward.

1. Firstly, you need to know that less is more and if medical history discourages it an antidepressant should be discontinued in all cycling mood people
2. Secondly, 70% of bipolar people will require 2 medications to stabilize their mood one to give them energy and one to help them sleep.
3. Abrupt discontinuations (except for Paxil and Effexor) can occur by starting the FDA medications for bipolar depression Seroquel XR and Prozac/Zyprexa combination
4. Abrupt discontinuations (except for Paxil and Effexor) can occur by starting combinations of an energizing mood stabilizer and a mood stabilizer to promote sleep
5. A slow taper of an antidepressant should be done when only one mood stabilizer is switched to such as Lithium or Abilify. Then, ideally at the rate by which the antidepressant was titrated up should guide its taper downward.
The worried mother
She is a married mother of 2 children who developed visual hallucinations of seeing bugs on her car windshield while taking antidepressant monotherapy and she was given a diagnosis of Bipolar one disorder. She has had severe panic attacks which has made flying on aircraft challenging for her and she has had periods of worrying for greater than two hours a day which has left her dysfunctional. She gradually developed worries that others were having thoughts about harming her over the last 2 months and she says she feels paranoid. She weighs 219 pounds and is 5’7” tall.

Current medications
LI2CO3 ER 450mg bedtime
Geodon 60mg am
Pristiq 50mg bedtime

She tried increasing the dose of her Pristiq to 100mg for a few days but this was not helpful for her as it usually is.

What do you want to do?
• Increase Geodon?
• Increase Lithium?
• Increase Pristiq?

There is always a risk of akathisia in people who take an atypical antipsychotic and I did not want her to experience any more anxiety than she is already experiencing. I recommended that she take an extra one time dose of Lithium ER 450mg 2 at bedtime once to help her stop worrying and help her fall asleep faster. I asked her to see if she developed a hand tremor and told her to eat extra food with her lithium to prevent her from getting stomach upset.

What I will do better next time
• Consider using benzodiazepines more when an emergency situation exists
• Encourage the use of decaffeinated coffee more frequently
• Involve the spouse more in the treatment plan
• After 8 years the case goes on

Differentiating central peripheral symptoms from central anxiety symptoms

<table>
<thead>
<tr>
<th>Panic symptoms vs. worrying for more than 2 hours a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
</tr>
<tr>
<td>SSRIs</td>
</tr>
<tr>
<td>SNRIs</td>
</tr>
<tr>
<td>Atypicals</td>
</tr>
<tr>
<td>Alpha 2 deltas</td>
</tr>
</tbody>
</table>

The telecom worker
Question: What is the diagnosis of a man who feels that voices are being sent to him by high frequency communication by an unknown entity?

Question: Can you treat delusional disorder with medications?

Question: Should he stay on his medications to prevent a recurrence of his depression even if his fixed delusional thoughts are not being helped by medications?

He is a 46 year old currently disabled man I initially treated in 1992 at a local mental health center who reported having auditory hallucinations of a negative nature commenting on his actions. He had periods of depressed mood and I treated him with desipramine and Navane. He entered my private practice on Zoloft and I had placed him on Abilify which helped the voices by his report a scant 20%. He did stay on the medications, however, as he did understand that the medications prevented his depression from returning. His diagnosis remains unclear but he is either suffering from schizophrenia or has a delusional disorder. He longer notices a difference in the intensity of the voices off of medications. He clearly has a diagnosis of Mood disorder and has a psychotic condition which would give him a diagnosis of schizoaffective disorder. He reports having a family history of amyotropic lateral sclerosis and does not know how the family member with that illness is being treated. His response to using a cannabinoid receptor antagonist was that his voices got worse. He reports not using cannabis now but I have my concerns about his use.

Cannabis and psychosis

Cannabis increases the risk of psychotic symptoms in individuals from the general population

In patients with established psychotic disorder, cannabis
-Has a negative effect on illness course
-Causes more and earlier relapses
-Causes more frequent hospitalizations
-Causes poorer psych social functioning
-Causes loss of brain tissue at twice the rate of patients with schizophrenia who do not use cannabis

Stahl et al.,

What I will do better next time
• Consider a lithium trial
• Don’t argue with a delusional person
• You can’t treat a fixed delusion with medications
• You treat these people symptomatically
• Give them support
• Consider long acting injectable Abilify when it hits the market
• After 20 years the case goes on

The project manager

Question: How do you restart Lithium therapy after an upper GI bleed induced by lithium?
He is a 58 year old father of 2 project manager with multiple medical problems including being overweight, sleep apnea Barret’s esophagus and hypothyroidism. He is a recovering alcoholic and is involved with AA. He initially presented to me with feelings that he could read people’s minds in the audience while lecturing to them. He carries a diagnosis of bipolar one. He had been treated with Wellbutrin and developed a cycling mood on it. He most recently was stable on Li2CO3 300mg 2 bedtime until he developed an upper GI bleed which sent him to the emergency room with a severely orthostatic blood pressure. I had managed him on Lamictal at 300mg am and this caused him to have some word finding and word switching cognitive problems which improved with reduction of Lamictal but caused him to become more depressed. Stimulants improved his cognition and his depression but he was opposed to using them on a regular basis. He took Ambien for a month which he “liked too much” and would not take it anymore. His thoughts would race at night before he went to sleep and he reported that this “noise” he had in his head responded to listening to NPR at night so he could get to sleep. Seroquel helped him sleep at 25 mg ½ bedtime but he was intolerant of higher doses which made him groggy. Zyprexa helped him sleep at 1.25mg bedtime but higher doses made him groggy and hungry.

He dropped out of my practice to see another psychiatrist and asked for my records which I brought to the physician’s office. I consulted with the physician and told the new doctor that he probably would need to be restarted on Lithium with the lowest possible effective sustained release dose possible. This case occurred before Saphris, Latuda and Fanapt were available.

What I will do better next time
• Understand that there is always a risk of nausea with taking a lithium salt on an empty stomach
• Consider a proton pump inhibitor
• Saphris, Latuda, Fanapt and Abilify are all options

Lithium
• Enhance BDNF – brain derived neurotrophic growth factor
• Inhibits the enzyme Glycogen Synthase Kinase GSK – 3 a pro-apoptotic enzyme highly expressed in hippocampal neurons and involved with synaptic plasticity
• Increases expression of Bcl-2 a critical antiapoptotic protein
• Increases glutamate clearance and decreases glutamate release
• Acts directly on the signal transduction cascade
Corell et al.,

Divalproex/valproic Acid/valproate
• Enhance BDNF
• Inhibits Glycogen Synthase Kinase GSK – 3 a pro-apoptotic enzyme highly expressed in hippocampal neurons and involved in synaptic plasticity
• Increases expression of Bcl-2 a critical antiapoptotic protein
• Increase GABA activity and mimics the action of GABA at postsynaptic receptors
Corell et al.,
Food bugs

Question: Can a woman with schizophrenia and recent memory problems improve on L-methyl folate?

She is a 68 year old married mother two who presented to me in 1994 with the delusion that there were bugs in her food. I initially treated her with Haldol 5mg bedtime then Zyprexa 5mg bedtime when it hit the market. She had complicating hypothyroidism at the time of her initial presentation with me. She subsequently left my practice and came back years later after I had treated one of her sons for a similar chronic psychotic condition. She now presents with mild memory problems and is wondering if she is developing Alzheimer’s disease. In schizophrenia we see problems with memory formation and not with memory retention. She was under more strain as a result of caring for a husband who was infirmed. She appeared more tired than she usually is as I have known her over the years and although says she slept well, her eyes were not as bright as they had been. There are recent studies demonstrating that people who have the tt genotype of the MTHFR gene and COMT VAL VAL polymorphism are at increased risk of suffering from cognitive challenges seen on fMRI testing. I recommended that she try Deplin (L-Methyl folate) in order to see if her mood would lift as I thought that a depressed mood was the primary cause of her memory challenges.

Current medications:
Zyprexa 5mg ½ tablet on Saturday, Sunday, Tuesday, Wednesday, Thursday
Zyprexa 5mg 1 tablet on Mondays and Fridays
Deplin 15mg AM

What I will do better next time
• Continue to assess if a dose reduction in Zyprexa is needed to reduce the long term risk of tardive dyskinesia
• After 20 years the case goes on

The avid fast food enthusiast

Question: How do you motivate a morbidly obese man with sleep apnea who is an avid fast food enthusiast with hypertension to improve his lifestyle habits?

54 year old single government worker with a history of alcoholism and a single alcohol withdrawal seizure which occurred while stopped at a traffic light. He has multiple medical problems all of which could theoretically be reversed with improved lifestyle habits. In order to promote a change in his habits, I attempted to change his existing pattern of reward and attempted to give him a dopamine and norepinephrine acting medication to trick his brain into believing that a new associated pattern of behavior was responsible for the surge of dopamine and norepinephrine he was experiencing. None of my attempts to change his ingrained reward circuits was effective.

He has a long standing history of depression and his mood has been stable on trazadone 100mg bedtime and Effexor XR 150mg AM for years. Augmentation strategies with multiple assorted stimulants caused elevations in his blood pressure. Wellbutrin increased his blood pressure as did low dose desipramine. Modafanil had little effect. Strattera had little effect at 60mg. The benefits of treating a man with long term depression, a history of alcohol abuse and anxiety with an SNRI is that low dose stimulants can be added to try to help improve cognition. My concern in
this man has always been that the saturated fat in highly processed foods does not allow nerve cells to develop the permeability and efficiency of firing necessary for optimal functioning. He has been able to maintain and be promoted to a higher level government job as his medications and involvement with AA have kept him from drinking.

What I will do better next time
- Add omega – 3 –fatty acids to augment his antidepressants
- Consider Guanfacine ER to reduce his blood pressure and increase frontal lobe efficiency by increasing Glutamate activity
- Cognitive behavioral therapy
- Encourage daily salad to promote weight loss
- After 14 years the case goes on
- Consider weight watchers
- Walking or biking every AM

The diabetic mother
Question: Can Geodon be used in augmentation of Wellbutrin and Lexapro to treat a depression and elevated blood sugars associated with a low grade abdominal infection

42 year married mother of 1 new born with type 1 diabetes on Wellbutrin and Lexapro who has had a recent elevation of blood sugar elevated by an abdominal surgical infection and presents with insomnia and poor concentration and attention secondary to both central and physical anxiety. She has insomnia and a resting hand tremor. Her Hamilton depression scale is 20 and last week when she was well it was less than 7. She was given a one time dose of Geodon at 20mg to reduce her anxiety which it did within two hours with a call back. I then recommended that it be continued for one week while she was started on an antibiotic. Her sugars came down into the normal range from the 200s. The Geodon was then stopped. She would not have been able to be fully attentive to her child if she were placed on Ambien or a benzodiazepine as she was already fatigued. Sedating medications may have probably caused her to sleep most of the day and not be as active at the home. Sedating medications work through a histaminic or cholinergic/muscarinic mechanism of action.

What I’ll do better next time
- Availability of a biomarker in people should be used when you can and blood sugar in depressed diabetics is a good way to monitor the need for atypical anti-psychotic treatment and cessation of treatment
- Short duration Geodon can help people with diabetes in the face of an acute infection get recovery sleep to function during the day but not cause fatigue or sedation that can be caused by a benzodiazepine or sleep aid.
- The case goes on after 2 years

The diabetic business man
Question: When can you start to taper Abilify after an acute episode of depression associated with alcohol use?

Question: Can you use blood glucose levels as a bio-marker to assess hypothalamic-pituitary-adrenal axis stabilization to guide reduction in Abilify after augmentation therapy?
78 year old diabetic business unemployed with type 2 diabetes who was hospitalized after drinking alcohol and suffering from a depressive episode. He was placed on Abilify 5mg bedtime in add on therapy to Cymbalta 60mg bedtime. His blood sugars slowly started to improve after four months at which time he was tried on methylphenidate 20mg am once which helped his processing speed and then he was maintained on 10mg of methylphenidate as his Abilify was reduced. Blood sugar may be an indirect measure of the hypothalamic-pituitary-adrenal axis and level of stress hormone specifically cortisol someone with diabetes may have. Regulation of the hypothalamic-pituitary-axis neural network can be performed by using dopamine partial agonists in the short term in people subject to acute stress as a result of medical infection or cortisol level elevation. As his blood sugar improved I took this to mean that his depression improved and as his DLPFC circuits were inefficient, I treated him with a dopamine agonist that helped him with his energy level but not enough to cut back on his pot a day habit of drinking tea which makes his hands tremor. A state of hyper-arousal and sympathetic tone can be reduced and even blocked by serotonin dopamine antagonists like Geodon and Abilify but the application of these medications needs to be carefully used in the hands of experts.

- Slowly reduce Abilify to 5mg ¾ bedtime over the course of 2 months
- Have a cardiologist review whether using methylphenidate at 10mg in a diabetic is an ok thing to do
- Have him verify his fasting blood glucose level with his machine and synch to his ipod

What I will do better next time

- Always consider other options for TRD
- Encourage socialization
- Diet and exercise
- Test dose of Abilify to see if anxiety could be helped
- After one year the case goes on

---

### Options for treatment of TRD, treatment resistant depression

- Dextroamphetamine,
- Buspar,
- Deplin
- T4 T3
- augment with Abilify or Seroquel
- TMS
- Remeron
- Switch to maoi
- Psychotherapy
- Lunesta augmentation.
- Using measurement based care to treat and resolve symptoms
- Consider adding another antidepressant as a cheaper option to atypical augmentation.

---

The teacher*

Question: Can low dose Abilify stabilize a mood in a head injured person below 5mg daily and use Nuvigil 250mg ½ AM to help DLPFC inefficiency?
The professional is a 50 year old married teacher father of one son. He started having early depressive episodes at age six and carries a diagnosis of Bipolar type one. He has a history of profound cannabinoid receptor antagonist use 3 times daily throughout high school and stopped completely when he went to college. Had a long 7 year relationship with a college sweet heart which ended as a result of the stress of professional school and he became depressed and left the state to travel west and to do post graduate work teaching. Found postgraduate school very stressful. While living in a new city, he met another student and developed another episode of depression treated with desipramine 300mg developed hypomania and was placed on lithium with a TSH of 100 and creatinine which elevated to 1.4. Subsequently stopped lithium and was placed on Depakote 1500mg with levels in the 70s with good response in addition to Wellbutrin. He then took Lamictal with the Depakote and stopped the Wellbutrin. He then had some cognitive impairment in memory word finding and word switching and subsequently stopped Depakote. Lamictal was now at 400mg AM. At this dose he experienced dizziness and lightheadedness and suffered from 3 bike crashes which resulted in cracked helmets. He did not suffer from a loss of consciousness that he recalls in any of the crashes. Low dose Abilify at 1mg a day was started now increased to Abilify 3mg a day. He went off Lamictal as he saw a vast cognitive improvement off Lamictal. He started Nuvigil when he developed gout and was fatigued to the point of lying in bed all day long. On Nuvigil his improvement has been evident in his ability to read for 3 to 4 hours and comprehend long complex lectures. He is exercising 1 hour a day on average daily which improves his mood by 10%. He feels his Nuvigil helps his mood by 20% and the Abilify at a low dose helps his mood by 30%. He stopped drinking 6 shots of espresso coffee every am which he was able to do successfully without withdrawal headaches after starting Nuvigil. He was placed on Uloric 80mg for 2 months then backed down to 40mg am. After being treated with Uloric 80mg for 2 weeks, his blood pressure dropped by 10 points and his pulse by 20 points for unclear reasons. His resting morning pulse rate was 44. Typically, post traumatic stress disorder is not well treated with medications. He needs psychotherapy but finds bike riding more important. He feels his exercise, work and his religion have helped him have purpose in life. He is a good father to his son and husband to his wife. He will probably need lithium when he is depressed in the future and cannot ride his bike. Higher doses of Abilify do reduce his irritability but he fears gaining weight. His attention and concentration are good and he could probably tolerate higher doses of Nuvigil if needed however, Abilify would need to be increased as well as Nuvigil has a sulfur moiety on it and is an inducer of CYP 3A4.

Current medications
Abilify 2mg twice daily
Nuvigil 250mg ½ am
Uloric 40mg am

What other options does he have?

- Treatment and life is a long highway with a lot of stops and dips in the road
- Probably Abilify at 5mg is best dose to ensure mood stability but an antidepressant effect at this dose is suspect as the medication starts to lose its agonist properties in some people
- Another medication with agonist properties can give a 10 to 20% improvement in symptoms and exercise can afford another 10 to 20% improvement in depressive symptoms.
- CBT can help another 10 to 20%
• Diet can help mood about 10 to 20%
• A complete personalized treatment plan is needed to improve a life, a life style and a family

What I’ll do better next time
• Encourage maintaining an active healthy lifestyle
• Find out if gout crystals in kidneys can be dissolved by the body using medications such as uloric or allopurinol

The grocer
Question: can Trileptal in a diabetic man help with his poor impulse control or will it cause an inflammatory reaction?

George was a 27 year old grocer who had a stroke secondary to years of having type one diabetes and his stroke left him with a a tendency for having a labile mood crying spells and bouts of inappropriate laughter. His behavior at times was impulsive and he could hurl racial epithets at others at whim. He was arrested several times for disruptive behavior at stores but being in a wheelchair and having left hemiparesis did not make him a candidate for spending much time in jail nor getting treatment through group services. He was mostly left to his own devices and spent much of the day looking at porn. He had been managed on Prozac and was intolerant of the atypical antipsychotics but he may have been a candidate for Nudextra a combination therapy of dextromephorphan and quinidine which has been found to be very helpful with reducing mood liability in people with pseudo bulbar palsy secondary to neurologic challenges. New dextra which is dextromephorphan with quinidine has been helpful in people with pseudo bulbar palsy. Trileptal caused him to have an allergic reaction and swelling of his legs. Paxil did not change his weight appreciably.

What I’ll do better next time
• Consider Nudextra for pseudobulbar palsy in people with strokes and neurologic conditions who have emotional lability to their moods
• The newer atypical antipsychotics should work in diabetes like Geodon, Abilify and Latuda but the older ones may not work as well. Time will tell

The martial arts specialist
Question: Can low dose Abilify be used to reduce Xanax in a man with a cycling mood disorder on trileptal.

He is a 36 year old martial arts instructor who has had a history of mood swings and depression associated with anxiety long standing. At one point he was treated with Haldol in an emergency room and he had been treated with multiple antidepressants and mood stabilizers. Understandably, he has always been leery of using the atypical antipsychotics because of his past bad experience with Haldol which gave him significant extra pyramidal side effects. He presents with using Xanax 2mg am 2noon and 1 bedtime to treat the anxiety he has had with Wellbutrin sr 150mg every am. Trileptal has helped him sleep at night and he has no cognitive challenges on it at this dose. Being on an antidepressant has always caused his mood to cycle but being off of it has always led to depression. His end point should be his taking Lamictal 200mg am and Abilify 2mg every am so how do you get there?
• Slowly reduce the Wellbutrin first?
• Start Abilify 2mg ¼ am?
• Reduce Xanax?
• Add Neurontin?
• Start Lamictal?
• Start lithium low dose?
• Add Deplin?
• Use an emergency atypical such as Zyprexa and Seroquel?

This is what I did
I started Abilify 2mg ¼ am for one month so he was able to get off of his Xanax. If he identified
that the Abilify would help his low energy state on his rating scale he would be more likely to
follow through with it. The next month he says he is almost off the Xanax. I wrote for Neurontin
300mg three times daily which did not work as well for the anxiety but clearly helped calm him
down. He is reporting more job search stress and his mood is cycling and he is on Abilify 2mg ½
every am. I recommended he take a one time dose increase of Abilify to 5mg and then reduce his
dose to 2mg 1 every am. He learned that the Abilify at a higher dose helps him as an anti-anxiety
agent. I still think that Wellbutrin is causing his mood to cycle. Wellbutrin was touted as being one
of the least likely antidepressants to cause mood cycling based on a small case series but it made
it into the guidelines. The fact is that all antidepressants can cause mood cycling in predisposed
people. He is now starting a new job and needs to reduce the Wellbutrin SR which I reduced to ½
every am which should reduce his anxiety and mixed manic symptoms. I am still being vigilant
with maintaining his mood at a euthymic level. He is unlikely to get extrapyramidal side effects or
dystonia on Abilify as he is now taking Neurontin 300mg three times daily. He is quite anxious
now, however, despite taking Neurontin and I perceive him to be in a mixed manic state. I
anticipate that when his Wellbutrin is stopped he can be started on Lamictal and titrated upwards
to 200mg every am. Then his trileptal can be reduced. He needs to be exercising which should
help his depression by 10%. Stimulants, wake promoters, Deplin, and Guanfacine may help
depression by 10% each. He says he has not had a history of having closed head injury while
sparring but admits that he has had bruises to his face in the past suggestive of his possibly
having frontal temporal lobe bruising. I assess him to possibly have a predisposition to having a
seizure disorder given his martial arts fighting and this makes him a candidate for Lamictal
treatment. Lamictal can treat low energy states and prevent cycling episodes but is not a good
anti manic agent..

Current medications
Wellbutrin 150mg SR ½ am
Neurontin 300mg three times daily
Abilify 2mg ½ every am
Trileptal 300mg 2 bedtime

What I’ll do better next time
• He appears calmer and cognitively better but I won’t be satisfied until he can be
euthymic off of Wellbutrin.
• I don’t know how cognitively sound he will be on a combination of Trileptal and Lamictal
and he may be at risk of having a rash
• Emergency medications are always an option but he is concerned about gaining more
weight
• Consider getting gene testing to find out if he has the VAL Val form of the COMT polymorphism or the tt form of MTHFR or both
• Consider Lithium earlier
• Roffman and colleagues (2008) investigated the interaction between the genes for MTHFR and COMT genetic polymorphisms on the Wisconsin card sorting task in 185 schizophrenics and found that those individuals who had a high level of verbal errors had the VAL VAL homozygous gene and at least one copy of the MTHFR T allele.

The executive
Question: can you maintain someone with a cycling mood disorder and multiple sclerosis with Lamictal and Zypraxa longstanding. Does Lamictal brand name differ in efficacy from generic?

He is a 43 year old male with a long history of multiple sclerosis and has been treated with Lamictal 200mg twice daily, trazadone 100mg bedtime and Seroquel xr 400mg bedtime. He has been in significant pain secondary unclear reasons. He finds that he is losing weight and is more fatigued recently and is now feeling zombie-like. His Hamilton depression scale is 12.

Is his fatigue due to?
• Overindulging in narcotics
• Seroquel XR at 400mg hs
• Depression
• Multiple sclerosis

He does not admit to drug use and I prescribed Strattera as he was looking fatigued. He took Strattera 60mg a day. His depression got better by about 10% the next day and he had shaved and was looking better but was still not motivated at all. After a long session, he did admit to me that he was abusing his narcotics. Once he told me he was using more narcotics I referred him back to his primary care and his neurologist for follow up.

What I’ll do better next time
• If a change in mental status occurs, always ask the person if their Lamictal was changed from a brand name to a generic
• Nuvigil and Provigil may help with fatigue
• Multiple sclerosis exacerbations can have associated depressive and manic episodes associated with them and it is hard to separate this from bipolar disorder.

The Salesman
Question: can you trust a person who has taken multiple antidepressants on his own without it being prescribed for him? Non compliance clearly complicates treatment. People do lie but people also delude themselves into believing untruths.

He is a 42 year old religious married father of three who self treated 3 previous episodes of depression and anxiety with antidepressants. He stopped the medications when his symptoms improved. He initially reported non-response to the medications leading me to give him a diagnosis of bipolar disorder but a non-response to mood stabilizers and a second opinion warranted another antidepressant trial. Nortyptylene was used to follow blood levels to assess compliance.

Repeated episodes of panic and depression probably would be responsive to maois
How do new treatment guidelines affect his treatment today?

- Check nortyptylene blood levels on people to make sure they are taking their medications
- Drug levels will be available for Seroquel, Zyprexa Effexor in the future
- Just because someone says they did not respond to a medication it does not mean they took the medication

### Major depression treatment APA guidelines 2010

Level of clinical confidence 1 – 3 of augmentation options and level of confidence by consensus of expert opinion.

- Psychotherapy: level 1
- Second ADP: level 2
- Atypical: level 2
- T4 or T3: level 2
- Mood stabilizer: level 2
- Anticonvulsant: level 3
- Stimulant: level 3
- Omega 3: level 3
- Folate: level 3
- Anxiolytic: level 3

### What are the factors to be considered when choosing an antidepressant medication?

- Patient preference
- Nature of medication response to medication
- Relative efficacy and effectiveness
- Safety tolerability and anticipated side effects
- Co-morbid medical problems
- Potential drug interactions
- Half life
- Cost

The telecom guy

Question: Can Geodon be used off label to augment Pristiq in a man with problems relating to others.

He is a 38 year old information technology worker single no kids no alcohol no drugs who has been depressed for years and has had few relationships. He feels uncomfortable in social
situations and is easily distracted at work. He initially came to see me on long acting Prozac. Over the years his attention and concentration became impaired.

Current medications
Geodon 20mg AM
Pristiq 50mg bedtime
Adderall 20mg AM

His father died and he became depressed. What do you want to do?

- Increase Geodon?
- Increase Pristiq?
- Increase Adderall?

He increased Pristiq 50mg once for a day which helped relieve his symptoms of depression then was able to return back to 50mg a day. He was not able to verbally express to me his feelings regarding his father’s death.

- Pristiq may work to help people through an acute period
- Geodon at a low doses works through 4 serotonin sub receptors and does not start blocking D2 until 120mg
- Rating scales help people verbalize feelings they may not often be able to verbalize

Hands tremble

Question: can you use Provigil in a man with a seizure disorder who has a history of prostate cancer and depression.

He is a 49 year old married father and disabled telecom engineer who presents with a several year history of anxiety and recently became more stressed being on medical leave and facing having to care for a sick wife who suffers from a heart ailment. He is tremulous when he comes into my office and says he has a brother who has mood swings. At the time of my initial evaluation of him, I diagnosed him with panic attacks and started him on Xanax 0.5mg twice daily and he became better over the course of a month but then developed worsening symptoms of depression I continued him on Xanax and he felt better but developed more depressive symptoms. I prescribed Effexor for him and his hand tremor increased though his energy improved marginally. He reported having had blackouts in the past and He was seen by a neurologist who diagnosed a seizure disorder and placed him on topamax. He had developed prostate cancer for which he underwent surgery. Before his surgery he was switched to Pristiq at 50mg every bedtime which seemed to help his anxiety. Primidone at 50mg helped his hand tremor for a while but he reported having lost a 90 day supply of the medication and it was not to be found. One Christmas he developed a low energy state and I was able to get him energy by starting Provigil 200mg ¼ every am. To which he had a good response and was able to put his Christmas lights up which was something he had not done in years. He continues to take the Provigil which gives him a lot of energy he needs to take care of his wife.
Current medications
Pristiq 50mg bedtime
Provigil 200mg ¼ every AM

He comes in more severely anxious and depressed with a Hamilton depression scale of 22.

What do you do?
1. Tell him to take an additional Pristiq 50mg once in the evening and return to his previous dose,
2. Tell him to increase his Provigil 200mg to ½ every am

Here is what I did
I had data points to suggest that Pristiq was somewhat helpful to treat his depression and anxiety in the past but I am also concerned that a sustained increase in Pristiq may precipitate a seizure. So, I told him to increase his dose of Pristiq once to 100mg in a 24 hour period and return back to his previous dose of 50mg every evening. His anxiety and depression improved for about 5 days, he did not experience any blackouts or seizures associated with the increase. Provigil is not associated with seizures but does have a sulfur moiety on it and does carry a risk of rash and does represent more of an unknown option. Provigil may also make some people more anxious and can cause psychosis in predisposed individuals off of atypical antipsychotics.

What I will do better next time
• Understand that people in chronic pain do need to have a sense of control and he may be holding on to the primidone prescription as a way out of his pain
• Neurologists see the brain structurally and psychopharmacologists see it more in terms of neurotransmitters
• Risks taken to get people into remission do not need to be reckless
• Consider referral for TMS transcranial stimulation
• After 2 years the case goes on

The masseur
She is a 48 year old white twice divorced woman mother of 1 daughter who has had a history of Bipolar type one disorder and multiple hospitalizations. 5’7” and weighs 130. She has had ongoing memory problems long standing related to her lithium level. She became worse on Seroquel and she became worse on Geodon. She became manic on Nuvigil 250mg ¼ once and had a runny nose after taking it and felt she had an allergic reaction to it.

Current medications
Lamictal 200mg twice daily
Li2CO3 450mg ¾ bedtime
Risperdal 1mg 1 and ¼ bedtime

Her Hamilton depression scale is 30 and she was hospitalized at a local emergency room. Her mood has always cycled on antidepressant medications.

What do you want to do
1. Try a one time dose of Strattera 40mg ½ once
2. Try to increase the Lamictal
3. Reduce Risperdal
4. Increase Li2CO3 450mg ¾ bedtime

Here is what I did. I told the ER to give her a one time test dose of Strattera 40mg ½ am once which helped her kick out of her depression and she was hospitalized and placed on a standing order of Strattera 20mg am. Unfortunately, her insurance did not cover her Strattera. Her focus attention and concentration improved.

What will I do better next time

- Can I get neuropsychological testing in order to assess her thinking
- After 4 years the case goes on

The phone company employee
Mr. Smith is a 52 year old man with multiple sclerosis and Bipolar type one disorder who was convicted of molesting his 18 month old daughter in 2001. He was hospitalized and placed on Zyprexa and developed a severe depression which was responsive to Lamictal. He stayed in group sex offender treatment as his multiple sclerosis worsened and he became confined to a wheel chair. He is intolerant of hot weather and becomes weakened and fatigued when his air conditioning at the home is off. He was placed on Nuvigil with improvement in his energy level. He was stable on brand named Lamictal for years but developed a slow return of his depression when he was switched to generic by his insurance company.

Current medications
Zyprexa 10mg bedtime
Lamictal 100mg 2 ¼ am
Nuvigil 250mg ¼ am

For which indications will his insurance pay for Nuvigil?
1. Shift work disorder
2. Idiopathic hypersomnia
3. Narcolepsy
4. Obstructive sleep apnea adjunctive treatment

The map maker
He is a 50 year old married government employee with 2 teenage sons who has Bipolar type two disorder. His father had a massive cerebral stroke in his forties which disabled him and confined him to a wheel chair. He reported feeling unsatisfied at work working with computer hardware and sought to take on another job as a map maker creating maps for the tourist industry. He had periods of high productivity associated with irritability and alcohol use and had a DUI once in the past. He was started on Seroquel XR 200mg bedtime in addition to Lamictal 200mg every am with an excellent response. He snores which sometimes bothers his wife.

Current medications
Seroquel XR 200mg bedtime
Lamictal 200mg every am
He is sedated, fatigued and uses a cup of coffee in the morning to wake himself up. What do you want to do?

- Try Nuvigil once 250mg ¼ am?
- Reduce his Seroquel XR 200mg to ¾ bedtime?
- Reduce Lamictal 200mg am?

Here is what I did

I asked him to try Nuvigil 250mg ¼ once and warned him about the possibility of Steven Johnson’s syndrome and 3A4 liver enzyme induction possibly lowering his Seroquel level. I did this as many people may develop a rash in the future on Lamictal which can be difficult to assess.

If he had a positive response it may be that Nuvigil may be able to be used in place of Lamictal to treat his bipolar depression in the future if he became intolerant to Lamictal because of a rash.

- Involve the wife more in his care
- Encourage a sleep study earlier
- Diet and exercise to promote weight loss

The soldier

He is a 50 year old nurse in the military who has had an unstable bipolar type two mood disorder for years. He had a history of having had multiple concussions from skiing accidents and fractured his helmet once on icy snow. He is 215 lbs. and is 5’9” tall. He came into treatment on Effexor XR150mg hs, Trazodone 100mg ½ hs, Risperdal 0.5mg hs and Lamictal 100mg am. He was started on Abilify 2mg ¼ am and was able to stop the Risperdal and his attention and concentration improved by 10%. The next month he had some challenges sleeping and required an increase in his trazodone once to 100mg but then he was able to get back onto a regular sleep pattern. He had some word finding and word switching challenges on Lamictal so I increased his dose of Abilify 2mg to ¼ every am and was able to reduce his Lamictal down to 100mg ½ am. As his attention and concentration continued to be a challenge on a lower dose of Lamictal I started Adderall 15mg every am with improvement in his DLPFC symptoms and without mood instability. He is still having problems losing weight due to portion control problems and he is adherering to eating 10 ounces of salad daily.

Current medications

- Abilify 2mg ½ am
- Lamictal 100mg ½ am
- trazodone 100mg ½ hs
- Adderall 15mg am
- Effexor XR 150mg hs

How do you get this person to lose weight?

1. Have him buy a juicer
2. Weight watchers
3. No BRAT diet foods (bananas, rice, toast and apples are constipating)
4. No fat dairy fat products
5. No alcohol, no drugs, no fast food,

What I will do better next time

- Consider starting a stimulant earlier to improve cognition
Understand that withdrawal of Risperdal can lead to insomnia by unblocking sedating Histamine and Alpha one receptors
• After 2 years the case goes on

The Puerto Rican

She is a 69 year old thin woman with a Hispanic accent who is caring for her infirmed husband. She has had nightmares about water in the past when she has been very depressed and she was given Xanax 0.5mg twice daily in addition to Celexa 20mg bedtime. Her concentration attention and mood all worsened on Xanax and she became hopeless and helpless. I first stopped her Xanax by switching her to Neurontin 300mg 1 am and 2 bedtime and she had improvement in her physical anxiety symptoms but still manifest a low depressed mood. I gave her a one time dose of Abilify 2mg ½ once which elevated her mood and stopped her nightmares. Once she was in remission I saw her monthly and she was given Abilify 2mg ¼ once a month which enabled her to slowly reduce her Neurontin and finally stop it over 6 months. She is now being seen every three months. Her diet consists of fruits and vegetables especially avocados.

Current medications
Celexa 20mg am

What I will do better next time
• Meet with husband
• Encourage prayer, yoga and meditation practice earlier on
• Encourage eating a diet high in omega 3 fatty acids earlier on

The First Responder*

He is a 42 year old Emergency Medical Technician with bipolar I disorder and spent most of his younger years in a profound state of depression. He drank heavily as a college competitive swimmer at an eastern Ivy League school and self treated his mood swings with exercise. Zoloft made him wired and he got better on Lamictal which he took for years at 200mg but he would increase the dose when he had stress in his life to help him have more energy. I started 2mg Abilify at ¼ am and he was able to reduce his Lamictal to 200mg ¼ am with improvement in his cognition and his ability to study. He does snore and was promoted to a higher level managerial position. He is reporting to use several cans of mountain doo a day to keep his attention and concentration at a high level but he is irritable.

What do you want to do?
• Start Adderall?
• Start Ritalin?
• Start Nuvigil?
• Start Provigil?

I opted to start Nuvigil 250mg ¼ am and he noted improvement in his attention and concentration but felt that he was more irritable probably by Nuvigil acting as an inducer of 3A4 and reducing levels of Abilify. He is starting to sleep poorly after his son was born

What do you want to do?
• Do you increase Abilify 2mg 1 bedtime?
• Do you decrease Lamictal to 100mg ½ am?

I opted to increase his Abilify and his mood and sleep improved. I was subsequently able to further reduce his Lamictal to 50mg am.

Current medications
Abilify 2mg hs
Lamictal 100mg ½ am
Nuvigil 250mg ¼ am

What do you want to do now?
• Try to increase the Nuvigil while trying to decrease his Lamictal?
• Consider lithium should he develop depression in the future?
• The case goes on after 15 years

Getting pregnant
She is a young 21 year old bipolar type I woman who is looking for a new psychiatrist as she wants to get pregnant. She presents with no head injuries and is currently taking trileptal 300mg 2 bedtime, and Zoloft 100mg am. Her thoughts are mildly racing in my office and she is experiencing some word switching challenges on trileptal by my examination of her though she is not reporting any cognitive problems. I outlined a plan to see if we could stabilize her mood on Abilify to see if her trileptal could be reduced to the point where she was not having any cognitive problems. From a pregnancy point of view, trileptal represents the medication which is probably most likely to cause fetal malformations and its effect on neuronal development in unborn children is unknown. On the other hand, Zoloft is likely to destabilize her mood if she is on this medication alone during her pregnancy. There is a growing atypical antipsychotic pregnancy registry at www.womansmentalhealth.org which she was referred to. I recommended that she try Abilify for one month at 2mg ¼ am to see if her trileptal could be reduced and her attention and concentration improved. She did not come back to see me again.

What could I have done better?
• Enlisted the help of her accompanying companion to support a plan to use the lowest effective dose of medications to carry her through her pregnancy
• Explain the risks vs. benefits of her completely stopping all of her medication in an effort to get pregnant

The colorful child*
She is a 13 year old with a colorful family history of several people who have been successfully treated with lithium. She presents with insomnia, racing thoughts, irritability and anxiety and was offered Zyprexa in the hospital but refused. I started her on Abilify 2mg ¼ am which helped her anxiety but did not change her insomnia. She agreed to take Lithium and had improved on just 300mg one bedtime. She denies having escalated her dose of this medication from l2co3 300mg
once a day to two a day but had called in for earlier refills. The family does not want to pay the co
pays and wants you to simply call in prescriptions to the pharmacy.
What do you want to do?
• Prescribe Li2CO3 300mg 2 bedtime?
• Find out if she is really taking two a day?
• Find out if her mother is taking the lithium?
• After six months the case goes on?

The dental assistant*
She is a 47 year old married mother of two who has a diagnosis of bipolar type one disorder. She
is 250 and 5’9”. She has an essential tremor of her hands well treated with propranolol 20mg am.
She has a brother who was treated with Depakote for mood swings and severe panic symptoms
with good relief and a stable mood. She is on Depakote ER 500mg 2 ½ on Mondays,
Wednesdays, Fridays and Saturdays and 3 on Sunday, Saturday Tuesdays and Thursdays. She
wants to lose weight but is having a hard time doing so. Her CMRS shows her to have inattention
and concentration challenges so she was placed on Ritalin 10mg three times daily with
improvement. She is still having a hard time with losing weight and further dose reductions of
Depakote ER have led to her having a destabilized mood so I started Geodon 20mg hs which
helped cut her appetite but not enough to help her lose more weight. She underwent a gastric
stapling procedure and then she dropped out of treatment with me one year later.
What I will do better next time
• Consider earlier treatment with augmentation with Geodon
• Consider using higher doses of stimulant for weight loss
• Weight watchers to track food intake
• Consider that gastric stapling may not cause weight loss in some individuals

Sister of mercy*
She is a bipolar type one nun who works at a retirement home and who first presented to a local
psychiatric facility with mixed manic symptoms and psychosis after being treated with high dose
Effexor XR for depression and back pain. Her morphine pump which had helped stabilize her
mood had run out and she developed more pain and fatigue. I initially started treating her 15
years ago and she had been stable on Li2CO3 ER 450mg bedtime and Seroquel 100mg bedtime.
She developed elevations of her blood sugars about one year after starting Seroquel and Abilify
was slowly started and increased to 5mg 1 ½ bedtime with improvement in her mood and auditory
hallucinations. Over this time her Lithium was also able to be reduced. Fatigue has always been
a problem for sister as she often falls asleep during morning prayers. I added Nuvigil 250mg ¼
every am which helped keep her awake during prayers and she was able to reduce and finally
stop the Seroquel using Neurontin 100mg 4 times daily to treat her anxiety. Reducing the dose of
Seroquel in many people is a difficult accomplishment as a combination of Abilify a partial agonist,
and a wake promoter had to be used to overcome the lost norepinephrine effect from stopping the
Seroquel. Her blood sugars are in the 90 to 100 range and she is able to accomplish her
caretaking responsibilities at the home.

Hypothetical tardive dyskinesia case # 1
50 year old woman with paranoia comes in on Effexor XR 150mg bedtime with delusions regarding her husband spying on her and she was placed on Abilify augmentation for 2 years with an excellent response and then developed a rotating movement of her foot which continued for and progressed for 2 months.

Do you
1. Immediately diagnose tardive dyskinesia and stop the Abilify allowing it to self taper
2. Slowly taper the Abilify over the next 4 months to avoid a withdrawal dyskinesia
3. Discuss the risks vs. benefits associated with being off of an atypical antipsychotic
4. Consider Clozaril low dose at 12.5mg hs

The physician tapered the Abilify over the next 4 months with improvement in the movement disorder. She was no longer paranoid after that time.

**Hypothetical tardive dyskinesia case #2**
40 year old woman develops tongue movements after being treated with Abilify 2mg for 2 years. The Risperdal was immediately discontinued and the movements remained the same over the course of the next 4 months.

Do you
1. Try Vitamin E
2. Try Clozaril 12.5mg bedtime
3. Wait another month hoping the dopamine receptors in her striatum will reset themselves
4. Restart the Abilify at 0.5mg bedtime to see if the movements subside

**Hypothetical sleep apnea case #3**
20 year old man with morbid obesity and sleep apnea has bipolar depression. Does not use his CPAP machine and is doubling his dose of Seroquel XR 400mg hs to help him sleep at night. His wife calls you to tell you that her husband has been getting Ambien from another physician.

How do you want to proceed?
1. Give a one time test dose of Latuda 20mg once to see if he sleeps, then switch off of Seroquel and onto Latuda if it works
2. Inform his wife he has to use the CPAP
3. Consider Nuvigil or Provigil only if he is compliant with the CPAP

**The video gamer**
He is a 52 year old father of 2 teenagers who works for a local college as an IT consultant who has type one bipolar disorder. He had been on LICO3 300mg 3 bedtime Seroquel 3 ½ bedtime Lamictal 25mg am and Adderall 20mg am but had gained a significant amount of weight. He is 250 and 5'11". Attempts to reduce his Lithium resulted in a rapid onset of severe depression and he had a history of becoming overly energized on Lamictal at 50mg a day. The goal was to reduce his Seroquel to help him lose weight while maintaining euthymia. Over the course of two years Abilify was slowly increased to 40mg twice daily after an initial low test dose of a 20mg helped him relax. His Seroquel was slowly decreased using monthly Abilify 2mg one time dosing to help him sleep for about 3 to 5 days. He is slowly losing weight and his Adderall was able to be decreased to 15mg am.

**Our favorite Avon representative**
She is a 46 year old single customer sales representative for a sporting goods manufacturer who has bipolar I disorder. She is morbidly obese at 290 and she is 5’4”. She came in Lithium carbonate 300mg 3 bedtime, and Depakote 3000mg in the past now at 1500mg hs. She was started on Abilify 2mg am and over the course of several years she was able to stop the Depakote and is now taking LICO3 300mg ¼ hs, Geodon 80mg hs and Seroquel XR 200mg ¼ bedtime to help her sleep. She had been taking Vyvanse at one time to improve her attention and concentration but her appetite did not seem to reduce and she did become irritable.

Current medications
Geodon 80mg hs
Seroquel XR 200mg ¼ hs
LICO300mg ¼ hs

The Golfer*
He is a 49 year old married construction worker father of 2 two teenage boys with bipolar type I who swam competitively in college and who has a severe bilateral essential tremor. He is 6’2” and 230. He had been treated with Depakote 500mg 3 bedtime, Propranolol 20mg am and LICO3 300mg ½ bedtime. Low dose Abilify was started at Abilify 2mg ¼ am and gradually titrated up to Abilify 5mg ½ every am. This enabled him to reduce his Depakote to 500mg 2 am with cognitive improvement such that he no longer had word finding and word switching challenges. His tremor continued to be severe and this was helped by his taking a higher dose of propranolol at 40mg every am. He noticed that his attention and concentration was greatly impaired and he was having challenges losing weight so he was started on Adderall 15mg am with a significant improvement in his hunger and he was able to lose a pound a week for several months. He finds that his exercise tolerance is decreased with Lithium but it helps decrease his gambling cravings. His golf game dramatically improved on Adderall.

The gambler*
He is a 36 year old single salesman for a local energy company who has a diagnosis of type I Bipolar disorder who was treated with Seroquel 200mg bedtime, Lamictal 400mg am. He has problems with impulsive gambling often losing hundreds of dollars and sometimes thousands. He was started on Abilify 2mg ¼ am and his dose was slowly increased to 2mg bedtime and he was able to reduce his Lamictal to 200mg am. He found that his gambling urges were helped by LI2CO3 300mg ¼ hs.

Current medications
Lamictal 200mg am
Abilify 2mg bedtime
LI2CO3 300mg ¼ hs

The lonely daughter*
She is a married mother of a 26 year old girl. She has a diagnosis of bipolar I disorder. She lost her father to suicide as a child and was the one to find him in the garage of the home after he had left the car engine running. She had resulting episodes of depression and was hospitalized and placed on Effexor XR which helped her but she developed a rash and had to discontinue it. She had been on multiple antidepressants but developed visual hallucinations. Her mood has been mostly stable with the help of Lamictal at 200mg and she sleeps at night with Zolpidem 10mg bedtime. She had required high doses of Lamictal in the past and these doses were reduced by using once a week Saphris 10mg ¼ bedtime to help her sleep and energy. Weight gain prompted a switch to Latuda and she takes 40mg ¼ bedtime which is helping her to lose weight.
Current Medications
Lamictal 200mg am
Zolpidem 10mg hs
Latuda 40mg ¼ am
Saphris 10mg ¼ bedtime once a week.

Chapter four
Future directions

Schizophrenia
We say that in people who lack the ability to look within themselves suffer from a lack of insight into themselves. We may also say that they have an inability to appreciate the emotions of others. We see this in an illness called schizophrenia which is a neuro developmental disorder which starts at age 8 or 12 but does not usually present until age 18 to 22. The first break of a schizophrenic is most responsive to medications and subsequent episodes become harder to treat for many. We do not understand why some people may have an initially good response to a medication and gain insight to have a good prognosis yet others fail to gain insight into their illness. It may be that our ability to have our frontal cortex observe the underlying sub cortical structures is inefficient in schizophrenia. In this illness, persons are unable to differentiate underlying sub cortical sensory stimulation usually in the form of visual or auditory experience from the reality of their own physical environment. To treat this inefficiency, we use medications to block dopamine receptors for a minimum of 2 hours a day at 70 to 80 % occupancy which somehow allows the cortex to communicate better with the underlying cortical structures. It is thought that hyperactivity in the meso limbic tract creates a physiologic state where consciousness cannot discern hallucinations and delusions from externally generated perceptions. By dampening down this hyperactive meso limbic tract, the higher cortical tracts can better regulate and monitor sub cortical structures through inhibition. Abilify is a third generation atypical antipsychotic medication which unlike other atypical antipsychotics is a partial agonist at D2 receptors and has a higher affinity at D2 than the other 12 atypical antipsychotics we currently have available. By binding with high affinity to meso limbic pathway D2 receptors at a low dose many unopposed meso limbic derived symptoms can be managed without concern of a manic episode happening. If manic symptoms do happen, a one time dose elevation to 10mg or the approximate dose that blocks 70 to 80 % of D2 receptors in the brain can shut down the mesolimbic pathway and instill a transient zombie like state for a few hours if necessary to save a life, a relationship or a career if necessary.

Early prodromal schizophrenia can manifest as challenges in many neural circuits and can present in a disguised form as bipolar disorder, attention deficit disorder, obsessive compulsive disorder and many other illnesses. There are many illnesses in which psychosis is an associated feature and these include mania, depression, cognitive disorders and Alzheimer’s dementia. There are many illnesses where psychosis is the defining feature such as schizophrenia, substance abuse disorders, delusional disorder, and brief psychotic disorder.

We do not know the exact underlying mechanism which is the cause for psychotic disorders. It is probably best to look at schizophrenia as a neuro developmental illness which has its beginnings 10 years before the diagnosis making it similar to Alzheimer’ syndrome. Our current treatment of psychosis at this time is based on the blocking dopamine receptors with 70% occupancy with medications for 2 hours a day over a 24 hour time period. We understand schizophrenia to be an
illness therefore where there is an elevated dopamine state responsible for positive symptoms and the same may be true for many different psychotic disorders. We are beginning to understand that this simplistic way of looking at psychosis is not that clear, however. The meso limbic pathway is responsible for psychotic symptoms that we see in the illnesses that have psychosis as their defining feature and in illnesses in which psychosis is an associated feature. Excessive dopamine firing from the brain stem of dopamine releasing neurons causes paranoia delusions and hallucinations. These symptoms occur sub cortically making it impossible for our frontal cortex to be able to discern what is real and not real in relation to our external environment. The meso cortical dopamine pathway will have a difficult time assessing underlying structures if it is operating with low level dopamine firing levels. The current glutamate theory of schizophrenia has evolved from our understanding of people who have had phencyclidine and ketamine induced psychosis. In this model, glutamate the major excitatory neurotransmitter is operating at a low level in the dorso lateral prefrontal cortex and this drives dopamine levels to be high in the meso limbic pathway to try to stimulate glutamate action. The result of this low level of dopamine firing is that cognitive symptoms of inattention and poor concentration occur in the meso cortical pathway. There are probably many reasons as to why there are varying levels of dopamine release in various different pathways in the brain. Susceptibility genes which code for the proteins that make the receptors, synaptic connections and growth factors needed to form connections correctly in the brain are responsible for connectivity challenges seen in psychotic disorders. Much of our learning manifests by our ability of the NMDA receptor to function properly. The NMDA receptor is implicated in new learning and is a coincidence receptor such that it requires activation by glutamate, glycine and depolarization to fire. Glutamate is the major amino acid excitatory neurotransmitter in the brain and is a precursor to the major inhibitory amino acid in the brain GABA gama aminobutyric acid. In the developing brain, it may be that excitatory glutamate input from our senses gets modulated through the NMDA receptors to teach inhibitory GABA neurons how to inhibit appropriately. It may be that failure to form these neural connections early in neurodevelopment may result in the many anomalies we see associated with schizophrenia. We may see visual system gating problems as well as auditory system gating problems. In schizophrenia we can see minor physical anomalies indicative of genes that have been turned on or maybe off inappropriately. Neural networks are such that ordinarily, GABA inhibitory interneuron’s reduces firing of meso limbic dopamine neurons. As a result of NMDA hypo function, this inhibitory action in the meso limbic pathway does not occur and excess firing occurs. The inhibitory action of GABA interneurons is stimulated by glutamate release and under conditions of NMDA hypo function or low glutamate levels dopamine firing in the meso limbic pathway is unopposed.

We can say in general that functioning varies from person to person. We can assume that we are all 100% at birth to puberty barring toxin in utero exposure. We can see that some people who are destined to develop schizophrenia are more likely to have physical and minor motor anomalies associated with gait, coordination, and can have challenges with posture. The brain at an early age may have suffered in these individuals an environmental insult or a genetic insult in utero that may account for these anomalies before or during conception. Men over 40 are at increased risk of having schizophrenic offspring as aging sperm DNA can deteriorate but can also be methylated, acetylated or phosphorylated. There are many opportunities for prenatal, postnatal infectious or traumatic events to occur which may lead to schizophrenia. Many of these insults are due to factors that reduce blood flow or oxygen to the brain. All of these insults seem to occur in schizophrenia during this phase of illness. When kids start to develop odd, anxious or withdrawn behavior and they look prodromal, parents take their kids to a therapist with the
concern that their child is moody or has ill temperament initially. The kids may start using substances. These prodromal symptoms occur between the ages of 13 to 18 yet they don't have delusions or hallucinations. These adolescents can appear more guarded and appear to be suspicions. They start showing cognitive deficits and teachers may comment on a student's declining grades. Some studies in schizophrenia show that grade performance goes down at ages 8 to 11 and they develop psychosis ten years later at age 18. A first break may occur at college with the combined stress of final exams, sleep deprivation or a new relationship. It may be that a low glutamate state drives negative symptoms and start early to cause cognitive deterioration and social withdrawal before the positive symptoms start happening. Unfortunately, we don't tend to treat these kids while they are having prodromal symptoms. We usually have to wait until these kids get admitted to the hospital before we make the diagnosis when they could be getting treatment early on. The delusions and hallucinations schizophrenics have are the manifestations of positive symptoms a manifestation of an elevated dopamine state in the meso limbic sub cortical pathways. This represents a new phase of the illness which started a decade before. The problem with treating a neuro developmental sub cortical illness that is hidden from detection from the frontal lobes is lack of awareness or the ability to self observe that usually occurs seamlessly and easily in most people with intact neural networks. If we could provide someone with 100% insight such that we could have people stay on their medications after their first index episode of psychosis many clinicians know that the rate of relapse would be reduced greatly. We know from past Intramuscular involuntary long acting injection studies that people were able to stay out of the hospital for long periods of time. We have decades of studies showing that intramuscular injections of dopamine antagonists keep people with schizophrenia out of hospitals and functioning. It is when people stop taking their medications they relapse. They stop taking their medications because they cannot self observe the fact that they need medications or find the medications intolerable. A disconnect between the observing cortex and the underlying sub cortical structures causes hospitalizations. In the context of a relationship with a therapist or a doctor compliance rates are increased. After the first episode or hospitalization many people will stop their medications and will not do well in the long term. After every relapse there is a progressive downhill course. Psychosis is bad for the brain and causes more stress on an already stressed system. Many people with schizophrenia will have a decline in functioning from 100 % to 30 % if they are not compliant with medications and if they have 5 or 6 episodes over the first few years. Some physicians wonder if the decline that happens in schizophrenia can be avoided with complete compliance and I believe that this is true. The ongoing processes that result in deterioration are multi-factorial and may include free radicals, apoptotic factors, and general inefficiency of neural networks. The toxic nature of psychosis is related to tissue destruction in many ways that are complex. It is unfortunate that many people give up on schizophrenics when there is always hope that these people can live useful lives and can work in capacities above which others may believe possible. Many people can recover from a bad psychotic episode. It may take one year to two years for them to come back. The brain recovers slowly from tissue damage and people with psychosis need time to heal and get better. They can go back to work and back to school. People with schizophrenia tend to live on the margin of society disabled and dysfunctional dependent on the welfare of society. We can see a tremendous response in some outliers to treatment in the beginning on the order of 87% response. It may take months for them to get well. 30% of schizophrenics are treatment resistant yet Clozaril prescriptions total about 3% of all antipsychotic prescriptions. The 13 % of schizophrenica who do not get better will probably go on to need Clozaril which seems to work better for people with treatment resistant schizophrenia. Clozaril does not work any better than other antipsychotics for a first episode of psychosis. Antipsychotics shine initially with first episode
After a while, resistance to several antipsychotics can develop which is unfortunate. Once they relapse again, getting a response again is not as easy as the first time. Second psychotic episode response is about 70% third episode is about 50%. The people get more treatment resistant with every relapse because of atrophy and tissue loss there may also be inflammatory changes that go on in the brain that are unknown. The development of treatment resistance is an unfortunate occurrence. Multiple antipsychotics with varying mechanisms of action may be tried with some response. As time goes on then you have to start using higher doses and you may get more side effects. The side effects then produce more non-adherences and it becomes a vicious cycle as they stop the medication again and again. By treating fully and consistently you can get the best outcomes. We can see in some people improvement in the negative and cognitive symptoms as a result of long term treatment with the atypicals. Underlying structural integrity of the brain is necessary for cognitive improvement to occur to a clinically significant degree. Stability with respect to functioning at home, work and in relationships requires a good doctor patient relationship. The questions that we should be asking is if the prodromal symptoms can be diagnostic and the answer is that we all have at times prodromal symptoms which are not diagnostic. 70 to 80 % of people who are normal have what can be called pre-psychotic symptoms such as superstitions, irritability or distractibility. The prodromal phase is not a time when you can definitively make a diagnosis. In the DSM 5 there may be an at risk diagnostic criteria for schizophrenia. It is important to know that not all people with prodromal symptoms switch to psychosis. Around the world people with prodromal symptoms have about a 30% conversion rate. By ten years 70% in one study of prodromal people converted to schizophrenia. So there are many who do not switch and this is a result of the mind and the brain being amazingly adaptable. Labels we give do not always hold up as the mind and brain will adapt to prove us wrong. It is possible to improve the functioning of our brain by consistently taking care of it. Working with a health care provider you can trust can help immensely. We need biomarkers to help us determine a future course of illness when a presentation is uncertain. We can measure cerebral blood volume to see the extent to which the ca1 region of the hippocampus is involved with memory formation. The hippocampus connects to all regions of the brain. The connections between the hippocampus and the prefrontal cortex are particularly strong making frontal temporal connectivity important. The connections with the thalamic filter are also critical for us to delete the massive amount of sensory information we receive from our multiple senses every second. The connections with the cerebellum are critical for fluidity of thought as well as motor coordination. Neurogenesis and neuroplasticity takes place in the dentate gyrus of the hippocampus. The PANSS is a scale used to follow negative and positive symptoms of schizophrenia and takes an hour to fill out. A score of 80 describes a very dysfunctional person. An improvement of 50 % is an indicator of marked improvement and is used by clinicians to communicate their impressions of a person. Around the world the risk of schizophrenia is 1% and is consistent across cultures. Most of the genes related to having an increased risk of schizophrenia are hard to find in a culturally diverse population as they seem to be buried. We believe that there are hundreds of risk genes for schizophrenia; the more you have the higher your risk of developing the illness. Many of the genes noted regulate glutamate receptors. COMT metabolizes dopamine and MAO-I also metabolizes dopamine. We have 20,000 to 30,000 genes in the brain. 15,000 or 50% of the genes in DNA are related to brain structure and development. Neuroplasticity, axonal sprouting, are all related to brain connectivity. Without this connectivity the brain does not function as an integrated unit. The genes related to neuroplasticity have many different names and include disc 1 and dysbindin and may lead to a loss in brain tissue if expressed as they may cause a loss in connectivity. Normal development requires connectivity and we have redundant backup systems to enable an inefficient circuit to function at
an improved rate unless damage by a toxin or other insult occurs like a viral infection. If a small part of our brain becomes damaged it may not become a big deal. It is a big deal when a disconnect occurs between the hippocampus and frontal cortex connection. This type of massive disruption can make a big difference clinically. People with schizophrenia have a hard time forming new memories. Once formed, they can remember very well. The people with psychotic bipolar disorders have the same overlapping genes as the people with schizophrenia. They seem to be related both to disconnectivity and the NMDA receptor. If you look at twin studies involving twins with schizophrenia, having one twin with schizophrenia incurs a 50% risk of the second twin having schizophrenia; it is not 100%. The concept of epigenetics and the principle of genes being turned on and turned off is very important in the development of schizophrenia. The environment plays a huge role in our neuronal development as does genetics. If two parents have schizophrenia the risk to the child having schizophrenia is 50% not 100%.

Who is at risk of psychosis

- People who have had brief periods of psychosis are more likely to experience them in the future
- Having schizotypal personality disorder or first degree relatives with the disorder and decline in functioning
- Minor psychotic experiences with in the past year

Neuropsychological functioning in ultra high risk of psychosis

- Global decreased neuropsych functioning in seen in people who develop a chronic psychotic disorder
- Processing speed is reduced in people with chronic psychosis compared to normal controls
- Verbal learning and memory are reduced in people with chronic psychotic conditions
- Visual spatial functioning is spared
- Verbal memory deficits maybe secondary to prefrontal-hippocampal neuro-developmental abnormalities
- Neurocognitive problems are uncorrelated with positive symptoms
- Neurocognitive deficits may be only minimally improved with antipsychotics if at all.

Stahl et al.,
Reduced Neuro cortical connectivity is already set at birth in schizophrenia, but a psychotic break occurs because of pruning or environmental insult. The diagnosis most likely to develop schizophrenia is impulse control disorder NOS, ADHD and bipolar NOS.

Bipolar disorder

Everyone has mood swings and it is the degree to which mood swings makes us dysfunctional in our lives that determines a diagnosis. Mood swings range from the euphoric irrational exuberance felt by an entire nation to the deepest darkest depths of despair that a lonely individual can experience. While there has never been much of a debate since Aristotle that mood swings exist in adults controversy exists in studies today if they occur in children. Assuming that they do and it is a real entity in children forces us to assess to carefully assess how to treat it and make dysfunctional children become our hope for the future. We can generally separate Type one mood swing people from type two people by mania which is best described as a excessively high energy state often accompanied by irritability and accompanied always by racing thoughts. A lower degree of mania is referred to as hypomania and is indicative of type two mood
swings. On a spectrum, all mood stabilizers will treat these illnesses but to do so safely and without medical complications while addressing cognition constitutes the art and science of medicine.

There are small enclaves of physicians around the United States who have developed an expertise in treating bipolar type 1 disorder with Lithium as a monotherapy device and we can learn a lot from studying these datasets. It appears that bipolar kids may not have a euphoric mood that is necessary for the diagnosis in some diagnostic criteria but what is very apparent in all groups is a sense of frustration intolerance that is driven primarily by a thought process that race faster than a speeding bullet. Racing thoughts are a foreign entity to most people who have not had the subjective experience of thoughts that jump from topic to topic. This distinct way of thinking seems to breeds true. This manner of thinking is often associated with an unbridled sense of optimism as one believes that anything is possible. In a sense, anything is possible when infinite possibilities can occur in the connections between thoughts. Connections between thoughts that can be made in one persons mind may or may not exist in the minds of others. Therefore, it may be that the carefully defined process of thoughts that race by jumping from topic to topic must be carefully explained to a person and a history elicited for an early onset of Bipolar disorder type 1 disorder to be made. Once the diagnosis is made by confirming that this core symptom exists, then a decision can be made as to which medication or medications to use. Lithium at its lowest possible effective dose can be used for type one mood swings as monotherapy in about 10% of cases. Mixed symptoms of depression and mania represent a more challenging form to treat and an atypical with the best cardio metabolic parameters available for an individual should be provide as first line. Lithium has been touted as causing many cases of renal dysfunction and hypothyroidism. Many instances of hypothyroidism do remit when lithium is discontinued whereas renal dysfunction does not reverse as fibrosis is a non-reversible phenomenon at this time. The amount of lithium needed to work effectively in a nerve cell is probably small compared to the circulating blood level needed to treat acute cases of mania. It may be that 1/4 of a Li2CO3 300mg tablet given daily may be enough to keep a constant intracellular level of intra neuronal lithium available to enable synaptogenesis and Neuroplasticity plasticity active to protect against the factors that make bipolar disorder so susceptible to variations in circadian rhythm, steroid hormones, hormone deregulation, and environmental stress. Higher blood levels of lithium at 1.0 can cause cognitive challenges for many people and may result in people not taking their Lithium as prescribed. It is probably best to have people taking a lower dose of lithium which can be rapidly increased if needed than for them to not take it at all. A consistent low dose daily of lithium provides for a small amount of lithium to be available to neurons intracellularly which can rapidly be elevated if need to prevent a manic episode from occurring. It is generally understood that it can take lithium several days to enter nerve cells for it to be effective when someone presents in a high energy state. This level can be increased more rapidly if someone is already taking a low dose and the ion is present in the nerve cell. The tragedy of bipolar disorder is the fact that a majority of people with bipolar1 spend an inordinate amount of time in a depressed state and this can be responsible for much of the lack of productivity and misery we see in the work place. Having a consistent energy level is not easy to accomplish in people with bipolar depression. Psychosis and mania can be treated by knocking people out for three days but keeping a mood stable and level requires fine tuning of medications and finesse.

There are many schools of thought on the use of antidepressants and bipolar disorder. It is not clear to me if a transporter blocking medication can rapidly increase synaptogenesis through...
hormonal variation or not in a predisposed individual and if this is in line with other factors resulting in an unopposed high energy state. In general, it is best to use at least 2 medications in the treatment of people who have a cycling mood disorder one that can be used to promote an energy increase at a low dose and another which can provide sleep. 70% people with bipolar disorder about require the use of two medications. Only about 10% of people who are bipolar can be maintained on lithium monotherapy and these people are typically bipolar type one.

A history of having cycling mood changes precipitated by circadian rhythms disruptions, steroid use, antidepressant induced cycling, and post partum depression can all lead to a concern about someone having a cycling mood. Antidepressants as a result need to be used sparingly as it is easy to deregulate a mood inadvertently by their use in individuals. I have used a one time dose of antidepressant in people who have a cycling mood and who have been depressed to get them up out of a depression. Many times this has lead to their cycling mood worsening. Bipolar type one disorder people who come out of a depressive episode acutely after a one time dose of an antidepressant may find themselves deregulated if they follow their rating scale for a while. It is for this reason that I am reluctant to follow them if they are maintained on an antidepressant for any significant period of time. Medications such as Lexapro seem to help with anxiety acutely and a one time dose can be helpful for this purpose but a cycling mood can be initiated even on a very low dose of a very selective serotonin reuptake inhibitor. Continued use can lead to mood cycling probably as a result of logarithmically explosive synaptogenesis that may occur after a few weeks of treatment driven by BDNF and growth factors. The use of low dose Lithium may be helpful in brain injured people with mood swings and depression who have sensitivity to mood cycling as they may be intolerant of higher doses. A self rating scale a third party observer and careful attention to depressive symptoms using a Hamilton depression scale will afford the best possible outcome for these people long term. The careful observing experienced physician who has been blessed with the opportunity to treat even one of these people has learned that consistent treatment can afford a lifetime of productivity in the form of a stable mood.

The unmet need; treatment of acutely suicidal people
There is an unmet need for people with acute suicidal ideation and many groups have been using IV ketamine off label to treat acute depression. The best general treatment we have at this time in people however to acutely stop orbito frontal depressive symptoms is the use of Abilify initially at a low dose in addition to an ssris or snri to improve antidepressant effect quickly. This algorithm is based on an analysis of data that suggests that Abilify works in augmentation with a signal in one week when added to an ssri. In the augmentation studies using Abilify, we do not know if Abilify is helping the antidepressant to work better or if the antidepressant is helping the Abilify to work better. This paradigm shift is the result of my using Abilify first line in acutely suicidal people at a maximal top end dose first to see if a response can be had first before starting an ssri. Our standard treatment for major depression takes far too long to work and people who are not naive to medications may want a faster onset of effect like IV ketamine has. The problem with IV ketamine is that although it works to stop suicidal thoughts in hours, its effect makes people have 2 sub- syndromes of schizophrenia including cognitive and positive symptoms. The currently available medications we have at this time to treat treatment resistant depression is Zyprexa and Prozac and vagal nerve stimulation. Ketamine helps with suicidal behaviors for one or two hours and this is its benefit. In the future, we will be using medications utilizing multiple mechanisms of action at once to treat the acutely suicidal. Lamictal probably works as an agonist blocking glutamate release and it takes too long to start working effectively. We wonder if many of our
treatments for depression already work by blocking glutamate release. Giving ketamine blocks glutamate release in many places in the brain including places that you do not want to block it. NR2B are more selective mglur agonists. Depression is a state of over active glutamate action in some specific pathways. If you can then stop glutamate in these pathways you could keep a person from entering a low energy state. Deplin may be able to help cognitive symptoms in schizophrenia if a person has the VAL VAL form of COMT and the t form of the MTHFR genes you might see cognitive improvement that would be helpful. ECT probably works by turning on all the glutamate in the brain where glutamate is probably forced out of a lot of different areas and this bombardment of glutamate of the brain may be akin to rebooting a computer. What you are doing is either shutting it down or over activating it. Once this happens you go back to endogenous rhythms inherent in our biologic systems and this allows the brain to reset its neurotransmitter systems. Agonists at the GABA receptor may play a role in the prevention of schizophrenia in the future. Schizophrenics may have a specific interneuron that does not work very well that usually makes GABA and because it is not controlling glutamate. Theoretically, lorazepam with its long half life seems to help schizophrenics and Xanax does not. We do not know if this is this anti anxiety effect or if it is because of a long half. High doses of Xanax with its short half life do not work well in schizophrenia. We know that gabapentin works and we know the backup medication we give to schizophrenics in the hospital is always lorazepam and it seems to work very well. It may be that they act by functioning in the place of dysfunctional GABA interneurons. NAC (n-acetyl cysteine) is linked to the glutamate transporters and some of their precursors and have been used in cocaine addiction. Changing the amount of glutamate and glycine in neural networks it is not as powerful as acting on the processes themselves that synthesis, reuptake them or destroy them. If we think of the drugs that are the most potent drugs in our practices the reuptake blockers like the ssris and the enzyme inhibitors like MAOIs are most powerful. You need grams of an agonist in order to modify a system in a minor way.

Intelligence-What happens next?
Intelligence is not defined by behavior as much as it is defined by our ability to make predictions about what will happen in the future in our world. Intelligence is a combination of many factors including imagination, perception, education and reasoning ability. All of us have different levels of abilities that we were born with and can train to develop. Our brain perceives the world in sequences and patterns which we remember and recall. When we match these patterns up against the reality that we face in our lives we make predictions all the time about an infinite number of outcomes. Our actions are our attempt to guide what happens in the future to be suitable for ourselves and our families. The internal matrix that guides our thinking and values is helps us raise our children. We ask ourselves continuously to understand what is going on so we can decide and make decisions based on memory and then take or inhibit action. While you are reading this book, you are making predictions about what I am about to write and you are making a prediction about what I am going to say next at the end of every sentence. This is the output of the neocortex and this prediction leads to intelligent behavior. An old brain such as a reptilian brain has sophisticated highly attuned senses designed to perform highly complex acts like fight flight, or freeze. The neocortex is a wrinkly layer of the brain that is shoved into a hard skull and over lays the old brain to control these complex functions. The neocortex memorizes everything like an ongoing camcorder in our early childhood development and by the time we are teenagers the neurons which are used regularly remain but those that die off by apoptosis fade. The neocortex takes information about the people we see and the places we’ve been to and encodes them in a hierarchal order which facilitates memory and enables us to remember. Memory is the recreation of past experiences by the synchronous firing of neurons that were involved in the
original experience and this is done in a framework of time, space and sequence. The neocortex allows us to then predict the future and when we judge this accurately, we call it intelligence. If you see something familiar and you say I have seen this before you can predict what happens next. Information then feeds back into the brain from our senses and allows us to make another prediction. Nature took the sensory information from the back of the brain and put it in the front to give us motor control of our behavior and planning ability guided by the prefrontal cortex. Our eyes scan the environment so when we look at a face we first look at the eyes then the nose. A change in the symmetry of a face is alerting and we are finely attuned to noticing fine variations in facial expression. Phasic neuronal firing appears to occur as the brain recognizes an altered pattern of our memory of a face for example. A more complete brain theory may therefore be based on a memory framework or how we store patterns and sequences in our head.

In the future, we need to prepare ourselves for the fact that in our search for cognitive enhancement products to care for an aging and more dementia prevalent society, that a medicine may be able to accelerate memory formation, memory recall and improve the efficiency of our prefrontal cortex.

Appendix A

<table>
<thead>
<tr>
<th>Treatment plan for a better brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No alcohol, no drugs, no fast food, (subway is ok) No saturated dairy fat, fruit, veggy, high fiber 50 grams with vitamin supplement or brewer’s yeast, hydration diet</td>
</tr>
<tr>
<td>2. salad 10oz. a day, oatmeal, almonds, green tea, wild Alaskan salmon</td>
</tr>
<tr>
<td>3. diet and exercise</td>
</tr>
<tr>
<td>4. barrier method for birth control</td>
</tr>
<tr>
<td>5. medication list with driver’s license</td>
</tr>
<tr>
<td>6. office hour availability m-f 8:30 to 5:30 sat 10 to 4</td>
</tr>
<tr>
<td>7. hospital telephone number for emergencies</td>
</tr>
<tr>
<td>8. physician cell phone number</td>
</tr>
<tr>
<td>9. gluten free diet</td>
</tr>
<tr>
<td>10. Primary care follow up lab screening heavy metals, Drug blood levels mitochondrial functioning, genetic testing for COMT and MTHFR (methyltetrahydofolate reductase) fasting blood sugar, triglycerides</td>
</tr>
</tbody>
</table>

Appendix B.
Adapted from Stahl’s Prescriber’s guide

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA approvals</th>
<th>Indications (labels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride has no approvals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asenapine 3 approvals</td>
<td>Schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Bipolar mixed monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar manic monotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD
<table>
<thead>
<tr>
<th>Medicine</th>
<th>Approvals</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole DPA</td>
<td>15</td>
<td>Acute and maintenance schizophrenia&lt;br&gt;Adults&lt;br&gt;Bipolar mixed acute mono and adjunct&lt;br&gt;Bipolar manic acute mono and adjunct&lt;br&gt;Irritability associated with autistic disorder&lt;br&gt;Schizophrenia ages 13 and older&lt;br&gt;Maintaining stability in schizophrenia&lt;br&gt;Bipolar maintenance&lt;br&gt;Major depression (adjunctive)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>6</td>
<td>Partial complex seizures&lt;br&gt;Generalized tonic-clonic seizures&lt;br&gt;Mixed seizure patterns&lt;br&gt;Pain with true trigeminal neuralgia&lt;br&gt;Acute/mixed manic (equetro)</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Strattera</td>
<td>2</td>
<td>ADHD in adults and children over 6</td>
</tr>
<tr>
<td>Wellbutrin</td>
<td>2</td>
<td>Major depression and smoking</td>
</tr>
<tr>
<td>Buspar</td>
<td>2</td>
<td>management of anxiety disorders&lt;br&gt;Short term treatment of symptoms of anxiety</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3</td>
<td>Treatment resistant schizophrenia&lt;br&gt;Reduction in risk of suicidal behavior in patients with Schizophrenia&lt;br&gt;Schizoaffective disorder</td>
</tr>
<tr>
<td>Cymbalata</td>
<td>2</td>
<td>Major depressive disorder&lt;br&gt;Diabetic peripheral neuropathic pain</td>
</tr>
<tr>
<td>Lexapro</td>
<td>2</td>
<td>Major depression&lt;br&gt;Generalized anxiety disorder</td>
</tr>
<tr>
<td>Neurontin gabapentin</td>
<td>1</td>
<td>Partial seizures with or without secondary generalization (adjunctive)</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1</td>
<td>maintenance treatment of bipolar 1&lt;br&gt;Partial seizures adjunctive and adults and children over the age of 2&lt;br&gt;Generalized seizures of lennox-gastaut syndrome adults and children over the age of 2</td>
</tr>
</tbody>
</table>
Conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine
Phenytoin phenobarbitol primidone or valproate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approvals</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>2</td>
<td>manic episodes of manic depressive illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance treatment for manic - depressive patients</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>1</td>
<td>schizophrenia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8</td>
<td>schizophrenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintaining response in schizophrenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute agitation associated with schizophrenia (intra muscular)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute mixed/manic monotherapy and Adjunct to lithium or Valproate</td>
</tr>
<tr>
<td>Symbyax Prozac/Zyprexa</td>
<td>1</td>
<td>Bipolar depression in combination</td>
</tr>
<tr>
<td>Oxcarbamazepine</td>
<td>4</td>
<td>Partial seizure in adults with epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial seizures in children ages 4 to 16</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintaining response in schizophrenia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>4</td>
<td>diabetic peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post herpetic neuralgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibromyalgias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial seizures in adults (adjunctive)</td>
</tr>
<tr>
<td>Seroquel XR</td>
<td>8</td>
<td>Acute schizophrenia quentiapine and Bipolar maintenance adjunct (quentiapine, quentiapine XR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar depression acute monotherapy (quentiapine, quentiapine xR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar mania acute mono and adjunct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar mixed acute mono and adjunct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major depressive disorder adjunct</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6</td>
<td>schizophrenia ages 13 and older IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delaying relapse in schizophrenia (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other psychotic disorder (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute mixed/manic mania, ages 10 and older (oral, monotherapy and adjunct to lithium or Valproate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>autism-related irritability in children 5 to 16</td>
</tr>
<tr>
<td>Drug</td>
<td>Approvals</td>
<td>Indications</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Topiramate | 4         | Partial onset seizures  
Adjunctive; adult and pediatric 2 to 16  
Primary generalized tonic-clonic seizures (adjunctive; adults and pediatric patients 2-26 years of age)  
Seizures associate with lennox-gastaut syndrome (2 years of age or older)  
Migraine prophylaxis |
| Valproate  | 6         | acute mania (divalproex)  
Mixed episodes (divalproex ER, valproic acid delayed-release)  
Complex partial seizures that occur in isolation or in association with other types of seizures (monotherapy and adjunctive)  
Simple and complex absence seizures (monotherapy and adjunctive)  
Multiple seizure types which include absence seizures (adjunctive)  
Migraine prophylaxis (divalproex, divalproex ER, valporic acid delayed release) |
| Ziprazidone| 8         | Schizophrenia acute and chronic  
Delaying relapse in schizophrenia  
Acute agitation in schizophrenia IM  
Acute mania/mixed mania  
Bipolar manic/mixed adjunctive maintenance |
### ADHD Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin methylphenidate</td>
<td>Concerta methylphenidate</td>
</tr>
<tr>
<td>Ritalin SR methylphenidate</td>
<td>Focalin dexamfetamine</td>
</tr>
<tr>
<td>Provigil modafinil</td>
<td>Modafinil</td>
</tr>
<tr>
<td>Modafinil</td>
<td></td>
</tr>
<tr>
<td>Ritalin SR</td>
<td></td>
</tr>
</tbody>
</table>

### Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lexapro escitalopram</td>
<td>Serzone nefazodone</td>
</tr>
<tr>
<td>Effexor XR venlafaxine</td>
<td>Tofranil imipramine</td>
</tr>
<tr>
<td>Cymbalta duloxetine</td>
<td>Elavil amitryptiline</td>
</tr>
<tr>
<td>Wellbutrin SR bupropion</td>
<td>Pameler nortryptiline</td>
</tr>
<tr>
<td>Remeron mirtazapine</td>
<td>Sinequan doxepine</td>
</tr>
<tr>
<td>Ascendin amoxapine</td>
<td>Parnate tranylcypromine</td>
</tr>
</tbody>
</table>

### Antianxiety Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspar buspirone</td>
<td>Ativan lorazepam</td>
</tr>
<tr>
<td>Valium diazepam</td>
<td>Klonopin clonazepam</td>
</tr>
</tbody>
</table>

### Mood Stabilizers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium carbonate</td>
<td>Tegretol carbamazepine</td>
</tr>
<tr>
<td>Depakote ER divalproex</td>
<td>Depakote IR divalproate</td>
</tr>
<tr>
<td>Zonagram zonisamide</td>
<td>Depakene valproic acid</td>
</tr>
<tr>
<td>Dilantin phenytoin</td>
<td>Primidone phenobarbitol</td>
</tr>
</tbody>
</table>

### Anti-psychotic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdal risperidone</td>
<td>Seroquel quetiapine</td>
</tr>
</tbody>
</table>
### Geodon Ziprasidone
- Abilify Aripipazole
- Haldol Haloperidol
- Loxitane Loxapine

### Clozaril Clozapine
- Orap Pimozide
- Navane Thiothixene
- Moban Molindone

### Zyprexa Olanzapine
- Thorazine Chlorpromazine
- Stellazine Trifluperazine
- Trilafon Perphenazine

### Fanapt Iloperidone
- Latuda Lurasidone
- Saphris Ascenapine
- Cariprazine

### Amisulpride Sulpride
- Symbyax Olanzapine/Fluoxetine

### Anti-Tic Hypertensive Medications
- Catapres Clonidine
- Tenex Guanfacine
- Inderal Propranolol

### Appendix D

#### Hamilton Psychiatric Rating Scale for Depression

- **Depressed mood**
  - 0 = Absent
  - 1 = These feeling states indicated only on questioning
  - 2 = These feeling states spontaneously reported verbally
  - 3 = Communicates feeling states nonverbally (i.e., through facial expression, posture, voice, and tendency to weep)
  - 4 = Patient reports virtually only these feeling states in his spontaneous verbal and nonverbal communication

- **Feelings of guilt**
  - 0 = Absent
  - 1 = Self-reproach, feels he has let people down
  - 2 = Wishes he were dead or any thoughts of possible death to self
  - 3 = Suicide ideas or gesture
  - 4 = Attempts at suicide (any serious attempts rates a 4)

- **Insomnia early**
  - 0 = No difficulty sleeping
  - 1 = Complains of occasional difficulty falling asleep (e.g., more than 30 minutes)

- **Insomnia middle**
  - 0 = No difficulty
  - 1 = Patient complains of being restless and disturbed during the night
  - 2 = Waking up during the night – any getting out of bed rates a 2 (except for voiding)
Insomnia late
0 = No difficulty
1 = Waking up in the early hours of the morning but goes back to sleep
2 = Unable to fall asleep again if he gets out of bed

Work and Activities
0 = No difficulty
1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2 = loss of interest in activity; hobbies or work – either directly reported by patient, or Indirect in listlessness and indecision (feels he has to push himself to work or activities)
3 = Decrease in actual time spent in activities or decrease in productivity.
4 = Stopped working because of current illness

Retardation (slowness of thought or speech; impaired ability to concentrate; decreased motor Activity)
0 = Normal speech and thought
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

Agitation
0 = None
1 = Fidgetiness
2 = Playing with hands, hair, etc.
3 = Moving about, can’t sit still
4 = Hand wringing, nail biting, hair pulling, biting of lips

Anxiety psychic
0 = no difficulty
1 = Subjective tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude apparent in face or speech
4 = Fears expressed without questioning

Anxiety Somatic
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

Physiological concomitants of anxiety (eg, dry mouth, wind, indigestion, diarrhea, cramps, belching, palpitations, headaches, hypertension, sighing, urinary frequency, sweating)
Somatic Symptoms – gastrointestinal
0 = None
1 = Loss of appetite
2 = Difficulty eating without encouragement; heavy feeling in abdomen
3 = Difficulty eating without encouragement; requests laxatives

Somatic Symptoms – General
0 = None
1 = Heaviness in limbs, back, or head; backaches, headaches, muscle aches; loss of energy and fatigability
2 = Any clear cut symptoms rates a 2

Genital symptoms (loss of libido, menstrual disturbances)
0 = Absent
1 = Mild
2 = Severe

Hypochondriasis
0 = Not present
1 = Self-absorption
2 = Preoccupation with health
3 = Frequent complaints, requests for help, etc.
4 = Hypochondriacal delusions

Loss of weight (rate either A or B)
A. When rating by history
   0 = No weight loss
   1 = probable weight loss associated with present illness
   2 = Definite (according to patient) weight loss
   3 = Not assessed
B. On weekly rating by psychiatrist, when actual weight changes are measured
   0 = Less than 1 lb. weight loss a week
   1 = Greater than 1 lb. weight loss a week
   2 = Greater than 2 lbs. weight loss in a week
   3 = Not assessed

Insight
0 = Acknowledges being depressed and ill
1 = Acknowledges illness but attributes cause to bad food, climate, over work, virus
   Need for rest, etc
2 = Denies being ill at all

Diurnal variation
A. Note whether symptoms are worse in the morning or evening.
   0 = No variation
   1 = Worse in AM
2 = Worse in PM
B. When present mark severity of variation
0 = None
1 = Mild
2 = Severe

Depersonalization and Derealization (feelings of unreality, nihilistic ideas)
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

Paranoid Symptoms
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution

Obsessional and Compulsive Symptoms
0 = Absent
1 = Mild
2 = Severe

Appendix E
Resources
Bipolar News.org
www.bipolarnews.org
Bipolar Significant Others
www.bpso.org
Bipolar Trials Network
www.bipolartrials.org
Child & Adolescent Bipolar Foundation (CABF)
www.cabf.org
Bipolar Disorder Information Center
www.mhsources.com/bipolar
Depression and Bipolar Support Alliance
www.dbsalliance.org
Expert Consensus Guidelines
www.psychguides.com
Juvenile Research Foundation
www.bpchildresearch.org
References


24. Seeman P: Dopamine D2 receptors as treatment targets in schizophrenia. Clinical Schizophrenia and related psychosis 2010 Apr vol 3 (1) 56-73


31. Mu: A single 20 mg dose of the full D1 agonist dihydrexidine (DAR-100) increases frontal perfusion in schizophrenia. Schizophr res 2007 Aug;94(1-3):332-41.


37. Kim: Calculating occupancy when one does not have a baseline: a comparison of different options. L Cereb blood Flow Metab 2011 Apr 27.


Index

Abilify (see aripiprazole)
Dopamine partial agonist
Adolescents 6, 21, 22, 80, 92
Alcohol 5, 17, 22, 35, 36, 45, 50, 57, 62, 63, 68, 77, 88, 95, 108, 113, 114, 115, 121, 124, 125
CMRS and 16
Amphetamine 16
CMRS and 16
Antidepressants 48, 59, 65, 93, 98, 100, 108, 120, 130, and 137
Antipsychotic drug potency chart 37
Aripiprazole (Abilify)
Low dose 33
Dosing 67, 78
Displaces Risperdal, Haldol 36
Multifunctional drug 35
Partial agonist 31
Reduces prolactin levels elevated by Risperdal 66
Test dose 36, 67, 74
Use in prolactinoma 36
Atypical antipsychotics (serotonin dopamine antagonist) 24, 144
Saphris (asenapine)
Latuda (lurasidone)
Fanapt (iloperidone)
Seroquel (quentiapine)
Zyprexa (olanzepine)
Risperdal (risperidone)
Geodon (ziprasidone)
Atypical antipsychotics (Dopamine partial agonists)
Abilify (aripiprazole)
Cariprazine
Benzodiazepines
Using Neurontin instead of 17
Bipolar Disorder Information Center website 148
Bipolar News website 148
Bipolar Significant Others website 148
Bipolar trials network website 148
Child & Adolescent Bipolar Foundation (CABF) website 148
Deep Brain Stimulation 26
Effexor XR 7, 25, 71, 80, 91, 109, 113, 122, 125, 128, 130, 144
Paxil 7, 71, 87, 88, 109, 117, 144
Switching
Atypical antipsychotics 6, 41, 80, 104, 107, 111, 116, 125, 127
Words on anticonvulsants 40, 64, 69, 73, 82, 83
Trazodone 125
Transcranial magnetic stimulation 26
Aggression 28, 79, 82
Agitation 36, 39, 40, 107, 141, 143
Akatheisia 40
Aripiprazole 40
Ziprazidone 40
Neurontin 17

Aripiprazole
  Partial agonist 31
  Low dose 33
  Test dose 36, 67, 74
  Dosing 67, 78
  Displaces Risperdal, Haldol 36
  Multifunctional drug 35
  Use in prolactinoma 36
  Reduces prolactin levels elevated by Risperdal 66

Risperidone
  Comparable doses 95, 96
Depakote 82, 83, 86, 87, 102, 103, 116, 128, 129, 130, 144
  GABA effect 86
  Irritability 121
Dose reduction chart 38, 65
Lithium 83, 86, 89, 94, 95, 96, 97, 98, 99, 100, 103, 105, 106, 109, 111, 112, 116, 118, 123, 127, 129, 136, 137, 142, 144
Tegretol 5, 9, 42, 64, 72, 83, 84, 85, 86, 103, 144
Lamictal 25, 26, 42, 69, 77, 78, 81, 85, 93, 94, 95, 96, 97, 98, 102, 102, 104, 105, 111, 116, 118, 119, 123, 125, 126, 127, 129, 130, 131, 138, 144
Assessment The clinical interview 62
Percentage in family practice setting 3
Cerebrovascular events in elderly using atypical antipsychotics 22
Childhood adolescent disorders 136
Cycling mood rating scale (CMRS) 54
  The seven subscales 11
  Functioning subscale 11
  Orbito frontal subscale (OFC) 12
  Mesocortical subscale (memory) 16 -18
  Dorso lateral prefrontal cortex subscale (DLPFC) (Attention concentration) 18 – 19
  Paradigm of mood stability 15
  Executive functioning subscale 19 – 20
    (planning) 19 - 20
  Motivation and fatigue subscale 20
  Use in medication reduction 56
  Use with a test dose 36
  Use in guiding medication choice 10
Cognitive effects of Mood stabilizers 40
Cortisol 20
Dementia 22, 30, 59, 61, 67, 80, 96, 131, 139
Depression and Bipolar Support Alliance website 148
Diabetes, Atypical antipsychotics in 37, 42, 68, 72, 74, 114, 1115, 117
Expert Consensus Guidelines website 148
GABA receptors
  Primidone irreversible binding 106
  Activity with Zyprexa 95
Activity with Depakote 112
Inhibitory interneuron action 132
Glucose 112, 114, 115
Hair loss 40
Haldol 37, 52, 107, 112, 149
Headache 12, 17, 35, 39, 42, 67, 116, 146
  With a test dose of Abilify 12, 35
Head injuries 56, 57, 58, 61, 62, 65, 67, 77, 118
Insomnia 20
  Benzodiazepine side effects on 40
Juvenile Research Foundation website 148
Lab testing 140
Neurontin
  Indications 141
  Off label use 66
  Replacing benzodiazepines off label 89, 102, 118, 125, 126
Medscape Psychiatry and Mental Health website 148
Methylphenidate 16, 60, 69, 115, 144
  CMRS and 16
Mortality in the elderly with dementia 22
Mortality in psychosis related dementia 22
NAMI (National Alliance for the Mentally Ill) 148
National Institute on Mental Health (NIMH) website 148
National Alliance for Research on Schizophrenia and Depression website 148
Nausea 12, 72, 73, 108
Nervousness 12, 13, 54
Number needed to harm 6
Number needed to treat 6
Nuvigil (Armodafanil) 15, 114, 123, 126, 127, 128
Obesity 129
Olanzepine (Zyprexa)
  GABA effect 95
Olanzepine and fluoxetine combination 144
Omega 3 fatty acids 18, 80, 105
Oxcarbamazepine trileptal 9, 126, 127, 144
Pain 63, 73, 102, 126
Parkinson's disease 24
Pediatric bipolar disorder 26
Paroxetine (see paxil)
Primidone 103, 141
Propranolol 53, 130
Prostate cancer 122
Quentiapine (see Seroquel) 5, 130, 142
Rapid cycling 39, 65, 108
Risperidone
  Comparable doses 95, 96
Schizophrenia 22, 33, 132, 142
Seizures 142, 143
<table>
<thead>
<tr>
<th>Functioning Scale</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medial Frontal Circuits</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Memory Circuits</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dorsolateral Prefrontal Attention Circuits</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor Control Circuits</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Executive Functioning Circuits</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Scores</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chart 4</th>
<th>Total Score</th>
<th>Almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>almost never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

The Art and Theory of Bipolar Disorder Medication Management by David R. Torres, MD