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Psychopharmacology/Sleep Disorders in Children and Adults

A. MEDICATION OVERVIEW: STIMULANT MEDICATIONS FOR ADHD

INTRODUCTION

Stimulant medications currently are used to treat the target symptoms of Attention Deficit Hyperactivity Disorder as well as similar symptoms, which may be seen in other disorders. Target symptoms include inattention, distractibility, restlessness and excessive motor activity as well as impulsivity. Such findings may be noted in Attention Deficit Disorder as well as in the autism spectrum where there may be associated inattention or motor restlessness.

Stimulant medication remains a highly effective treatment for ADHD with any one stimulant choice given at the right dose having a 70% likelihood of success. The non-stimulant Strattera tends to have a less robust response and requires a full month to become effective though is an option in children with significant tics as stimulant medication may exacerbate tics. Intuniv, another non-stimulant is highly effective in targeting impulsivity and motor restlessness, while somewhat less helpful in treating inattention. It may also treat tics.

Side effects of stimulant medication may include decreased appetite/sleep, slowing of growth rate, increased blood pressure/pulse, changes in mood, headache or stomach upset.

If a child has a history of structural heart defect, history of palpitations/chest pain/fainting episodes, murmur or family history of a heart attack/sudden death under age 50, a pediatric cardiology consultation should precede any consideration for stimulant medication. Obtaining blood pressure, pulse, height and weight as well as considering an EKG also is helpful. While medication treatment alone may be fully effective, it is important to note that up to two-thirds of patients with ADHD have comorbidity in regard to mood, anxiety, disruptive behavior or learning based difficulties. In these children, behavioral interventions are helpful in addition to medication treatment.

Stimulant medications as well as Strattera may slow the rate of growth and decrease weight. To avoid this, medication should be taken with food and high-energy snacks or supplements should be provided if appetite is diminished. It may also be reasonable to periodically hold stimulant medication on a weekend or long holiday if this effect is pronounced though ADHD symptoms would reemerge. Hence, food intake and growth are linked. Finally, an alternative treatment such as Intuniv may be a consideration when appetite and growth issues are very significant.

1. Ritalin (methylphenidate)
The maximal daily dosage of Ritalin is usually 60 mg. per day or 2 milligrams per kilogram per day whichever is less. Typically it is given in the morning and at lunch with an optional dose at 4 p.m. This dose may be ½ other doses to limit rebound symptoms and decreased appetite at dinner time. The medication works for about four hours when given in the regular form although Ritalin LA may last up to 8-hours. Other 8-hour preparations of Ritalin include Metadate and Methylin. Possible side effects include decreased appetite and possible increase in blood pressure or pulse. Also tics (eye blinking, throat clearing, and facial movements) may be seen when the child receives this stimulant medication. Ritalin may, "unmask" tics which a child may be prone to show even without Ritalin.

2. Ritalin LA (long acting); Metadate CD
These medications are also long-acting Ritalin preparations though with an 8-hour duration. For those children who experience insomnia with the Concerta which has up to 12-hour duration, the slightly shorter-acting stimulant medication, which can be given once daily, may be a good option. With Ritalin LA, half of the Ritalin dose is released immediately and the second half at lunch time. With Metadate CD, 70% of the dose is released initially and 30% subsequently. Both may be opened and sprinkled on food.

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3. Concerta (methylphenidate extended release)
Concerta is an extended release form of Ritalin which typically will last up to 12 hours with each dose. Of note is that after taking the medication in the morning, it does enter the system rather quickly during the first hour and then will continue to remain in the system for up to 12 hours. This provides much needed flexibility with dosing as the child does not then need to have Ritalin during lunch at school and most children will not need an afternoon dose of Ritalin. For those few children who begin to re-experience inattention, distractibility or impulsivity in the later afternoon, at times a low dose of short-acting Ritalin may be added around 4 or 5:00 p.m. Concerta works like Ritalin although the dosing is somewhat different. Concerta is initiated at 18 mg. in the morning and this is equal to receiving Ritalin 5 mg. three times a day. When increased to 36 mg. in the morning this is equal to taking Ritalin 10 mg. three times a day. Finally, the maximal dose of Concerta (under age 13) is 54 mg. in the morning and this is equal to taking Ritalin 15 mg. three times a day. For ages 13 and above the maximal dose of Concerta was approved to be up to 72 mg. a day and this is equal to taking Ritalin 20 mg. three times a day. Concerta may have similar side effects as Ritalin including a decrease in appetite or difficulties with sleep though it does appear generally to be well tolerated.

4. Quillivant (methylphenidate extended release-liquid form)
Quillivant is another extended release form of Ritalin which may be best tolerated by children who are unable to swallow a capsule tablet or open and sprinkle type medication. Quillivant will last up to 12 hours in duration. One ml is 5 mg. The dose may be adjusted upward based upon

the clinical response and side effects. Side effects may include headache or stomach upset, particularly the first week of treatment. Other common side effects include decreased appetite or possibly difficulty initiating sleep. For the small subgroup of children who do require a liquid form of medication for ADHD, this is a good alternative.

5. Adderall (L/D dextroamphetamine)
Adderall includes two different forms of Dexedrine. The short-acting dose range is usually up to 40 mg. per day or 1 milligram per kilogram per day whichever is less. It may last between four to six hours per day and may be given once or twice daily depending upon its effect. For some students, they may receive a morning dose and then a second dose around 3:00 or 3:30 p.m. avoiding the lunchtime dosage. Side effects are similar to Ritalin although the decease in appetite may be somewhat greater with this.

6. Adderall XR (extended release)
Adderall XR can be given once daily in the morning and will last for up to 10 to 12 hours daily. It is available in increments of 5 mg. to 30 mg. in dosing, and if the child is unable to swallow the capsule, the Adderall XR can be opened and sprinkled on food and ingested. It is an important stimulant option to the longer acting stimulant such as Concerta, in part because those children who do not respond to Concerta may respond to Adderall XR.

7. Dexedrine (dextroamphetamine)
Dexedrine has a usual maximal dosage of 40 mg. per day or 1 milligram per kilogram per day whichever is less. It is often given in the morning and at lunch with an optional afternoon dosage. The Dexedrine spansule, however, may be given once a day and has effectiveness up to six or eight hours. Side effects are similar to Ritalin though like Adderall, decreased appetite may be somewhat greater than Ritalin.

8. Vyvanse (long acting Dextroamphetamine)
Vyvanse has been marketed in part to provide treatment to those with an ADHD and substance use disorder. It is inactive until ingested and requires one hour to become effective. It remains active up to 12 hours. When broken down in the G.I. track, the active medication is a long-acting form of Dexedrine. Side effects are similar to other stimulants. The dose range is 30 mg. to 70 mg. daily.

9. Focalin (D-methylphenidate)
Focalin is the structural mirror image of Ritalin with a dose range of 5-30 mg. once daily. It may be given two or three times a day. For some children who do not respond to Ritalin, Focalin may be more effective. It has similar side effects as Ritalin. 5 mg. of Focalin is equal to 10 mg. of Ritalin.

10. Focalin XR
Focalin XR provides up to between 8 to 10 hours of Focalin when given in a single dose. In addition, it has been shown to be more effective than the other stimulants particularly early in the school day. The capsule may be opened and sprinkled over food for children who are unable to swallow the entire capsule. Focalin XR is available in dosages from 5 mg. to 30 mg. (maximal dose) daily. It is often considered for elementary school children who only require an 8-hour duration medicine. It does not usually interfere with appetite or sleep.

11. Daytrana (methylphenidate transdermal patch)
The Daytrana patch allows for Ritalin to be absorbed through the skin into the bloodstream directly. It is applied to the hip area, requires about two hours to become effective. When removed at the end of the day it remains in the bloodstream for an additional three (3) hours. Though possibly very convenient and helpful for those who cannot swallow medication, persistent skin reactions are common. If significant skin hypersensitivity occurs, the child may be unable to take other Ritalin-type medication in the future. Also, the D (active) L (less active, more side effects) isomers are absorbed into the blood stream without a GI first pass effect. Daytrana patches are available in 10 mg, 15, mg, 20mg. and 30 mg. doses. The 10 mg. patch is 27.5 mg. of Ritalin contained in the patch.

INDIVIDUALIZED TREATMENT WITH A STIMULANT MEDICATION

Using a 12-hour duration medication may be helpful particularly for children and adolescents where there is significant homework in the afternoon and early evening hours, and there is no reported sleep difficulty when taking the medication. Considering an 8 to 10 hour duration medication is reasonable if the child has diminished appetite around dinner or sleep difficulties with the 12-hour medication. Open and sprinkle formulations are effective if the child has trouble swallowing. For young children who require a relatively immediate onset of medication in the morning with limited after school homework, Focalin XR is a good choice. For older children and adolescents, 12-hour formulations including Concerta, Vyvanse or Adderall XR will be helpful throughout the day and into the early evening for homework. For adolescents or young adults with a history of substance abuse, Vyvanse may be a reasonable first choice given that there is limited abuse potential as it is an inactive compound until digested. Non-stimulant medications may be an option if stimulant medications are ineffective or if there are prominent tics. Short acting stimulant medication may be added in the morning in low dose to the 12-hour formulations to obtain a rapid response, or may be added at the end of the day to prolong the duration of the various long-acting medications. ADHD symptoms persist in 2/3 of all children into adolescence and adulthood. It would be reasonable to decrease or hold medication every 6 to 12 months to be certain that it remains necessary. Alternative/complimentary medications for ADHD have not been shown to be very effective. Children in the autism spectrum treated for ADHD symptoms tend to have a variable response and more side effects. If generic formulations are used these are generally within 20% potency of the brand name alternative. There may also be an interaction between Dexedrine, Adderall and Vyvanse with citrus fruit products, which may decrease the effectiveness of the medication.

B. MEDICATION OVERVIEW: NON-STIMULANT MEDICATIONS FOR ADHD

INTRODUCTION:

Although stimulant medications have been available for 50 years in treating ADHD and despite their success rate (i.e., up to a 85% success rate if 2 stimulants are attempted) the stimulant medications nonetheless may have side effects or may not be as effective as desired. In this case, non stimulant medications may be extremely helpful. The non-stimulant, Strattera is FDA approved though tends to have a less robust response than stimulant medications and takes up to

a month to become effective. Intuniv is another option, also FDA approved, very effective for impulsivity/hyperactivity and with a modest effect on attention/focus.

1. Strattera (atomoxetine)
Strattera is a non-stimulant medication which should be administered twice a day with food. The starting dose is generally 0.5 mg. per kilogram daily and this is increased gradually upward not to exceed 1.4 mg. per kilogram daily. Common side effects include sleepiness, stomach upset and headache. In children the maximal dose should not exceed 80 mg. a day and in adults it should not exceed 100 mg. a day. This medication is generally not as effective as stimulant medication and is usually used on a second-line basis. It may, however, be considered first-line in children with severe tics as it does not generally make these worse. Strattera may also increase blood pressure and pulse, requiring ongoing monitoring in this regard. Because Strattera may take a full month to become effective at a therapeutic dose, if transitioning from a stimulant medication, gradual cross-titration will be helpful because removing a stimulant medication suddenly will result in a full reemergence of ADHD symptoms. Prozac and Paxil may increase Strattera blood levels. The Strattera capsule should not be opened and sprinkled as this may increase stomach upset.

2. Intuniv (guanfacine extended release)
Intuniv is FDA approved for ADHD. It targets hyperactivity, impulsivity and outbursts/oppositional behavior. To a lesser extent, it enhances attention and focus. It may reduce tics and has no negative effect on appetite or growth. It may improve sleep and, indeed can cause drowsiness as a side effect. Other side effects include lightheadedness, decreased blood pressure and pulse. A baseline EKG and monitoring of vital signs is necessary. The dose range is 1-4 mg./day based on weight. It may require 3-4 weeks to be fully effective.

3. Wellbutrin (bupropion)
Wellbutrin is not FDA approved for use in children, nor is it FDA approved for ADHD. However, it has over the years become a second-line agent to the FDA treatments for ADHD. Wellbutrin is often initiated at approximately 3 mg. per kilogram daily not to exceed a final dose of 6 mg. per kilogram daily. It should never be given to a person with a history of an eating disorder or a seizure disorder. It has a 5% risk of rash, and may also cause an increase in anxiety and insomnia. Wellbutrin increases norepinephrine and dopamine in the brain which are the two neurotransmitters found to be low in ADHD. While the Wellbutrin SR requires twice a day dosing (maximal daily dose in adults, 400 mg. daily), Wellbutrin XL which is available in 150 mg. and 300 mg. doses can be given once daily.

4. Tenex (guanfacine)
Tenex has been used for over 10 years to treat impulsivity and hyperactivity though was not FDA approved for ADHD. A baseline EKG and vital sign checks should precede Tenex use. Tenex acts to stimulant the alpha-2 receptors in the brain. It also has been shown to decrease tics, which may be associated with ADHD. Short-acting Tenex may be started at 0.5 mg. at bedtime and increased/given in divided dose up to 2 mg. a day. Tenex is not associated with changes in appetite, weight or growth. Hence, children on stimulant medication who demonstrate a flattening of their growth curve or failure to gain weight may be considered for Tenex as an alternative.

5. Clonidine
Clonidine, like Tenex is an alpha-2 agonist in the brain and used to treat blood pressure in adults. Unlike Tenex it is shorter acting (needing two to four doses a day) and causes fatigue. Clonidine has been used to enhance sleep in children with ADHD. Like Tenex a baseline EKG and vital sign check is recommended before use.

6. Kapvay – A long acting form of Clonidine taken twice daily. It may cause more fatigue than Intuniv.

7. Provigil (modafinil)
Provigil was noted to show promise in treating ADHD but did not receive FDA approval due to a risk of possible serious skin rash. In teens and adults it is however, used to treat narcolepsy/excessive daytime fatigue.

C. MEDICATION OVERVIEW: ANTIDEPRESSANT MEDICATION

INTRODUCTION

Antidepressants are an important part of treatment in depression and anxiety. While different types of psychotherapy remain important as well, antidepressants have been shown to be effective in many depressive disorders including major depression and dysthymia. Anxiety disorders including panic disorder, obsessive compulsive, separation anxiety, social anxiety and generalized anxiety disorder also respond to medical treatment. Antidepressants differ based on the chemical messengers they increase in the brain. All antidepressants have about a 70 percent chance of working if given at the right dose for the right amount of time when treating depression.

The risk of suicidal ideation during the first 12-weeks of treatment with a serotonin reuptake inhibitor is 4% in depressed children or adolescents as opposed to a 2% risk due to placebo (a net 2% risk of suicidal ideation with antidepressants). The periods of greatest risk are:

1. Starting the medication.
2. Increasing the medication
3. Tapering/discontinuing the SSRI

The physical symptom most often associated with suicidal ideation and SSRI's is akathisia or intense motor restlessness and inability to sit still. Behaviorally, the child or adolescent may also appear agitated. As a result, the FDA has recommended gradual adjustment of medication with close monitoring. A concern in giving serotonin reuptake inhibitors includes the risk of triggering "bipolar switch" in children or adolescents. It is important to recognize that side effects may include:

1. Activation – very common almost immediately after starting the medication which would warrant considering an alternate SSRI or a more gradual dose adjustment. It presents as physical restlessness, mental restlessness, hyperactivity and disinhibition (also seen in 3 to 5% of children who take Benadryl.) Activation usually stops 24 to 48 hours after discontinuing the medication and is not a bipolar switch.

2. Bipolar Switching – this is far more rare than activation. It includes specific features of euphoria and grandiosity not just agitation or activation. Related findings may include a decreased need for sleep, pressured speech, racing thoughts and flight of ideas. Many children treated with SSRI's for anxiety or depression may exhibit activation and are mistakenly given a bipolar diagnosis and prescribed mood stabilizers and/or second generation antipsychotics. In such children, these medications may be tapered and discontinued.

3. Celebration – children and adolescents who show marked improvement in mood with reduced anxiety may indeed celebrate. While they may use occasional bad judgment no euphoria or grandiosity is evident. This too should be distinguished from the activation or bipolar switching and would not call for discontinuing the medication.

Medication treatment for depression should be geared to attain full remission of symptoms as opposed to simply a positive response. Medication is generally continued after the person is stable for a one year period in an effort to prevent relapse and then be slowly be tapered. Two episodes generally warrant a two-year duration of treatment and three episodes may require longer-term treatment. Cognitive behavioral therapy given in combination with a SSRI is more effective in treating depression and anxiety than either treatment typically is alone. Of note is if the primary caregiver is depressed, then such therapy for the child or adolescent will be less effective.

Common side effects of all SSRI's include stomach upset, changes in sleep pattern, headache as well as activation and bipolar switching noted above. At times, there may be an increase in sweating, and some difficulty with weight gain. In choosing an anti-depressant it is helpful to recognize if a parent or close family relative has benefited from a specific SSRI, this may be helpful for the child or adolescent as well. Medications with fewer drug interactions include Zoloft and Lexapro. Prozac has more drug interaction and has a longer duration of action. and remains effective even if periodic doses are missed. In addition, generic forms of serotonin reuptake inhibitors may not be of comparable potency despite similar dose. These medications generally require two to six weeks to begin to become effective. Health maintenance activities include exercise which reduces weight concerns and also improves mood. Substance use may prevent medications from being effective and contribute to a worsening of side effects.

1. Serotonin Selective Reuptake Inhibitors (SSRI's)
These medications have experienced widespread use in adult psychiatry and now are used in child psychiatry. Research efforts are underway to further support their usefulness and safety.

A. Prozac (fluoxetine) – Prozac was the first of the serotonin reuptake inhibitors to reach the American market in the late 1980's. The usual dose range in adults is up to 60 mg. for depression and up to 80 mg. per day for obsessive compulsive disorder. In children and adolescents, the dose range may be from 2 to 5 mg. in small children up to 40 to 60 mg. in adolescents. Prozac is FDA approved age 7 and above in treating depression. Of all the SSRI's, Prozac has the longest half-life and common side effects include headache, stomach upset, possibly an increase in restlessness, a sleep disturbance and sexual difficulties. It is given once a day usually in the morning. Prozac has also been

approved for use in Bulimia and has also been effective in binge eating disorder in adolescents. It is also available in liquid form.

B. Zoloft (sertraline) – Zoloft is FDA approved in adults for depression, obsessive compulsive disorder, panic disorder and post-traumatic stress disorder (PTSD). This medication has been FDA approved for use in children and adolescents for the treatment of obsessive compulsive disorder (age 6 and older). The dose range in adults is up to 200 mg. per day though in children it may be started at 12.5 mg. per day with a dose range typically up to 100-150 mg. in adolescents. Side effects include headache, sexual or sleep difficulties as seen with Prozac, as well as stomach upset. The nausea or diarrhea seen at times with Zoloft is usually brief but if troublesome, may require more gradual adjustment in dose or dividing doses. It has an intermediate half-life with lowering of dose done carefully when the medication is stopped. Zoloft also has little interaction with other medications.

C. Lexapro (escitalopram) - Lexapro is the chemical mirror image of Celexa. It appears to be more effective and potentially better tolerated than Celexa. 10 mg. of Lexapro is equivalent to 40 mg. of Celexa. The dose range of Lexapro in adults is 10 to 20 mg. daily. Lexapro is FDA approved age 12 and above often beginning at 5 mg. daily. Side effects may include headache, fatigue, stomach upset, sleep difficulties and sexual side effects. Lexapro does generally appear to be well tolerated and has minimal drug-drug interaction. It also has an intermediate half-life and is not typically associated with discontinuation symptoms.

D. Celexa (citalopram) – In adults the dose range is between 20 and 40 mg. with very limited data in its use in children or adolescents. The side effect profile appears favorable, though again with episodes of headache, stomach upset, restlessness, sleep or sexual difficulties possible. Celexa has little interaction with other medication. Doses above 40 mg. daily are not recommended due to EKG changes.

E. Paxil (paroxetine) – This is a very short half-life serotonin reuptake inhibitor which if stopped suddenly may cause some withdrawal symptoms. Sleepiness as well as weight gain has appeared to be more common with Paxil. Headache or stomach upset are usually brief. The dose range in adults is typically up to 50 mg. per day with dosages between 10-40 mg. more common if used in children or adolescents. It is also available in liquid form. Paxil CR (Continuous Release) may have less stomach upset (dose range 25-75 mg/day). Paxil has been FDA approved in adults for depression, obsessive compulsive disorder, panic disorder and social anxiety disorder. Due to the potential of serotonin discontinuation symptoms when Paxil is stopped, and because of case reports of increased self-injurious behavior, Paxil is **not** recommended by the FDA for children and adolescents.

F. Luvox (fluvoxamine) – This medication is FDA approved for use in adults, children (age 8 and above) and adolescents for obsessive compulsive disorder. Though not formally approved in the United States for the treatment of depression it is well recognized to be an effective antidepressant as well. The dose range is up to 300 mg. in adults with

dosing in children at 12.5 to 25 mg. and increased up to the 200 mg. range in adolescents. Once the dosage goes beyond 100 mg. given typically at night, it is then usually given in two doses (a.m., p.m.). Side effects such as headache, stomach upset and restlessness as well as difficulty with sleep and sexual functioning may take place. Important medication interactions include: Hismanal or Seldane (recently off the market) as well Propulsid, Theophylline and Xanax (or similar anxiety mediation) in combination with Luvox. Luvox CR (continuous release) is available for once daily dosing.

G. Anafranil (clomipramine) – This medication is within the tricyclic antidepressant category, a group of antidepressants which have been available since the 1960's. Anafranil first came into use in the US in the late 1980's and it is considered a highly effective treatment for obsessive compulsive disorder. The dose range in adults is up to 250 mg. per day while use in children and adolescents may range from 25-150 mg. per day. The major difficulty with Anafranil is its side effects. These include sleepiness, weight gain, dry mouth, blurred vision and constipation. In addition, because it may slow cardiac electrical condition or increase heart rate, a baseline EKG is helpful.

All SSRI's may cause a decrease in sexual desire and delay in orgasm. Lowering the dose or adding Wellbutrin may be used to decrease this.

2. Serotonin Norepinephrine Reuptake Inhibitor (SNRI):

a. Effexor (venlafaxine)
This medication has been used mostly in adults to treat depression though open studies in children and adolescents have shown it to be possibly effective in the treatment of attention deficit hyperactivity disorder as well as anxiety. The dose range in adults is up to 375 mg. in the short-acting form and 225 mg. per day in the sustained release form. Potential side effects include headache, stomach upset, sleep disturbance and sexual difficulties. In 5 percent of individuals, Effexor may increase blood pressure. Effexor has also been shown to be helpful in treating depression that does not improve with other medications. The FDA has approved Effexor for use in generalized anxiety disorder as well. The FDA recommends **avoiding** Effexor in children due to possible behavioral side effects.

b. Pristiq (desvenlafaxine)
This is a metabololite of Effexor, with a dose of 50 mg.

c. Cymbalta
This is an antidepressant FDA approved for use for adults though sometimes considered for adolescents. Like Effexor, it increases serotonin and Norepinephrine in the brain. However, Cymbalta has significant drug-drug interaction resulting in possible increases of blood levels of other medications taken. There also have been case reports of serious liver injury in those taking Cymbalta, and baseline as well as follow up liver enzyme testing will be helpful.

3. Agent which increases serotonin and norepinephrine in the brain Remeron (mirtazapine)

A. Remeron (mirtazapine) – Remeron has been used mostly in adults with a dose range of 15 to 45 mg. at bedtime. Remeron also increases sleepiness and increases appetite. It does not tend to cause sexual side effects and has little interaction with other drugs.

4. Agent which may increase norepinephrine and dopamine in the brain
Wellbutrin (bupropion)

Wellbutrin comes in short-acting, sustained release forms, and an extended release form. It is used for depression in adults though may be helpful in treating ADHD symptoms in children and adolescents as well. The maximal dose for the short-acting form and XL form is 450 mg. per day while it is 400 mg. per day in the sustained release SR form, both given in two divided doses. Wellbutrin XL (150mg./300 mg.) is taken once a day. Side effects may include headache, stomach upset, increased anxiety, decreased sleep and rash. Wellbutrin should not be given to those who have or had an eating disorder or seizure disorder. In adults, Wellbutrin has also been marketed as Zyban, the anti-smoking medication. It does not cause sexual difficulties and also may cause weight loss. It has little interaction with other medication.

5. Viibryd (Vilazodone) – For adult patients. Increases serotonin and targets serotonin receptors. Dose range 10-40 mg. May cause activation//drug interaction (e.g. erythromycin).

6. Trintellix (Vortioxetine)
This is another serotonin reuptake inhibitor-type medication that also will have an impact on the post synaptic serotonin receptor to enhance effectiveness. The dose range in adults may initiate at 10 mg daily (5 mg if the person is very sensitive to medication) and may be increased gradually, not to exceed 20 mg daily. Common side effects include stomach upset, headache, or dizziness. It may also have sexual side effects.

7. Fetzima (Levomilnacipran)
Fetzima is a newer serotonin norepinephrine reuptake inhibitor which tends to have a significant impact on norepinephrine in particular. The dose range begins at 20 mg daily and may be adjusted upward not to exceed 120 mg daily for adults. Common side effects include stomach upset, headache, and it may result in sexual side effects. There is also the potential of raising blood pressure which should be monitored during its use.

8. Tricyclic antidepressants Elavil (Amitriptyline), Tofranil (Imipramine), Sinequan (Doxepin), Pamelor (Nortriptyline), Norpramin (Desipramine)
Prior to the serotonin selective reuptake inhibitors in the late 1980's these medications were the main treatment for depression. Though effective, the side effects are troublesome and include sleepiness, lowering of blood pressure, constipation, dry mouth, blurred vision and difficulty with urination. For these reasons the tricyclic antidepressants are used in only a small group of adult patients not responding to other medications and have infrequent use in children and adolescents. Imipramine has been used in the past to treat enuresis (bed wetting).

9. Monoamine oxidase inhibitors (MAOI's)
These antidepressants include Nardil and Parnate. There is no current indication for use in child and adolescent psychiatry although in adults these medications have been used to treat

depression as well as panic disorder. Foods that contain tyramine (wine, aged cheese) must be avoided because the interaction of the medication with such foods may result in a significant increase in blood pressure. In addition, a number of over the counter medications should be avoided with this class of antidepressant (for example: antihistamines) to avoid a sharp increase in blood pressure.

D. MEDICATION OVERVIEW: MOOD STABILIZING MEDICATIONS

INTRODUCTION

Mood stabilizing medications are used in the treatment of bipolar disorder (manic depressive illness) as well as other disorders in which target symptoms of sudden shifts in mood, impulsivity or aggression are seen. Other disorders include: Intermittent Explosive Disorder, Cluster B Personality Disorders (borderline or antisocial personality disorders) and Disruptive Behavior Disorders with unstable mood (for example: ADHD or Conduct Disorder). These medications generally require a dosage adjustment over time, are given more than once a day and also are monitored with the use of blood levels.

Bipolar disorder in children is a very real condition which should be considered in the following instances:
1. Discrete episodes of euphoria/over exuberance, decreased need for sleep coupled with grandiosity and depressive episodes.
2. Family history of bipolar disorder.
3. Medication induced hypomania.

There is however, a trend to give a bipolar diagnosis to children with severe mood dysregulation (for example seen in ADHD) or in depressed children with a family history of bipolarity. As a result, medication combinations including mood stabilizers, antidepressants, ADHD-type treatments and atypical neuroleptics/antipsychotics may be taken by children. The risk of missing a bipolar diagnosis certainly results in impaired functioning at home, school and socially. However, multiple medications in situations where a bipolar diagnosis is misapplied may contribute to dramatic side effects. The National Institute of Mental Health urges caution in making this diagnosis and care in prescribing multiple medications.

1. Depakote (valproic acid)
Depakote has a dose range in adults generally between 1000 and 1500 mg. per day with a range in children and adolescents typically between 250 and 1000 mg. per day. The ideal blood level is between 50 and 100. Side effects include weight gain, sleepiness and stomach upset. In young girls and teens there has been concern about the possible risk of cysts on ovaries while using Depakote. The group of girls who may be at risk are those with significant body hair growth who are overweight. Polycystic ovary syndrome (PCOS) may result in a loss of menses, acne, and increased hair growth typically during the first year of Depakote treatment. Depakote may also suppress thyroid hormone to a mild degree.

Depakote is also available as an extended release preparation and this form of Depakote can be taken once at night yet have its full effect both in the day and evening. The advantage to this

type of dosing is that daytime sleepiness, stomach upset and hand tremor may all be decreased. When obtaining a blood level after using the Depakote extended release at night, typically the blood level should be done the following day in the late afternoon hours.

2. Lithium (lithium carbonate)
The dose range of Lithium in adults is typically between 900 and 1500 mg. per day while in children and adolescents this may be between 600 and 1200 mg. per day. Effective blood levels for most people are between 0.6 and 1.0. Side effects may include hand shaking, increased urination and weight gain. There may also be stomach upset and diarrhea. The thyroid may become less active and kidney may also be affected. Water pills (diuretics) given for high blood pressure and Motrin (ibuprofen) may increase Lithium levels. If Depakote or Seroquel are added to Lithium this may increase the risk of hypothyroidism. Lithium has also been shown to decrease the rate of suicide in bipolar patients.

3. Tegretol (carbamazepine)
The dose range of Tegretol in adults is typically 800 to 1200 mg. per day, though in adolescents this may be between 400 and 1000 mg. per day. The ideal blood level for most people is 8 to 12. Side effects may include weight gain, rash, sleepiness and stomach discomfort. Although Tegretol may produce a blood level, it activates the liver enzymes and may be broken down more quickly over time. Because of this, a higher dose may be needed to keep the same blood level. By activating liver enzymes, other medications may also break down quickly, decreasing their effects.

4. Trileptal (oxcarbamazepine)
Trileptal is an FDA approved antiseizure medication in childhood. It has not been shown to be highly effective in treating bipolar disorder based upon research studies. Unlike Tegretol it does not require a specific blood level and does not tend to decrease the blood count which may occur with Tegretol nor does it increase the activity level of the liver enzymes. It has nonetheless been used by some practitioners for mood stabilization at a starting dose between 150 and 300 mg. twice daily and titrated upward based upon weight and effectiveness to a range of 1200 mg. a day. Side effects include dizziness or difficulties with balance as well as fatigue. Within several weeks of beginning Trileptal a blood test for s serum sodium level should be done as in some instances Trileptal may decrease serum sodium.

5. Lamictal (lamotrigine)
Lamictal has been shown to be effective in treating bipolar disorder, particularly the depressed phase. Unlike Depakote it is not associated with polycystic ovary syndrome and unlike Lithium it is not associated with significant effects on the thyroid or kidney. However, Lamictal is often associated with a skin rash and in a small percentage of patients the rash may be serious. By starting the dose of medication very low, for example 12.5 mg. a day for the first two weeks and adjusting upward slowly (dose range 50 mg. to 200 mg. based upon age and weight) risk of rash is reduced. Common side effects include headache, stomach upset, dizziness and difficulties with balance or coordination.

6. Neurontin (gabapentin)
Neurontin has not been shown to be an effective mood stabilizer according to research studies.

Some practitioners have used this to assist with mood and anxiety. Neurontin does not require blood levels, has limited interaction with other medications and minimal breakdown by the liver. Common side effects include dizziness, sleepiness and stomach upset. The dose ranges in adults is between 1200 and 3600 mg. a day with lower doses used in teens.

7. Topamax (Topiramate)
Topamax has not been shown to be effective in mood stabilization or bipolar disorder according to research studies. It has, however, been used at times by physicians who attempt to stabilize mood while recognizing that Topamax may result in weight loss. Topamax has a 1 to 2 percent risk of causing kidney stones. A more common side effect is difficulty with memory.

E. MEDICATION OVERVIEW: NEUROLEPTIC (ANTIPSYCHOTIC) MEDICATION

INTRODUCTION

These medications have a role in treatment for adults and children to diminish thought disturbances (delusions and hallucinations) as well as bipolar disorder. In those without a thought disturbance, the neuroleptics have been used to decrease agitation and/or extremely unusual behaviors as well as serving to help medication treatment for obsessive compulsive disorder. They also decrease tics in the various tic disorders. This class of medication has also been shown to be effective in the various thought disorders (schizophrenia, schizo-affective disorder, mood disorder with psychotic features and delusional disorder). Finally, treatment of unusual behaviors and/or angry outbursts seen in the disruptive behavior disorders (for example ADHD) as well as the Autism spectrum.

Despite their effectiveness in stabilizing mood, diminishing unusual thoughts and agitation as well as treating tics, there have been side effects of concern related to the second generation antipsychotics. Weight gain, increased blood sugar/lipids, sleepiness and increases in serum prolactin may occur. When initiating these medications, modifying diet and increasing exercise are very important. Children and adolescents seem to enjoy the Wii fitness or physical activity programs. Healthy eating patterns include eating breakfast daily, avoiding juice drinks/soda and having healthy food options as snacks, also avoiding fast food, second helpings and saturated fats. Increased prolactin may result in decreased menses, breast enlargement/discharge, failure to enter or progress through puberty, hair growth in females and sexual side effects. Medications with the greatest risk of increasing prolactin include Risperdal, Zyprexa, Geodon and Seroquel. Abilify tends not to increase prolactin. Medications with the greatest effect on weight, lipids and blood sugar include Clozaril, followed by Zyprexa, Risperdal, Seroquel, Abilify and Geodon.

A. Second Generation Antipsychotics

1. Risperdal (risperidone): Risperdal comes in both a liquid and tablet form providing greater ease of administration and flexibility. The range in dose for adults is typically between 1 and 6 mg. For older adults and children the dose may be initiated at 0.25 to 0.5 mg. daily and increased gradually upward. Side effects include sleepiness, and at higher doses, possible restlessness or muscle stiffness. In the treatment of delusional thoughts (fixed false beliefs) or hallucinations (hearing or seeing things not really present) slow adjustment of medication will help to limit side effects. If muscle stiffness should become a concern, Cogentin is at

times added to the Risperdal to prevent this side effect. Risperdal may also be used with other medications. In obsessive compulsive disorder, it may be used to assist a serotonin reuptake inhibitor (for example: Zoloft, Luvox, Prozac, Paxil, Celexa). In the autism spectrum disorders, it may decrease unusual behaviors or periods of agitation in children who also may be treated with other medication. The FDA has approved Risperdal for treating aggression in autism spectrum age 5 and above. In monitoring Risperdal, periodic liver enzymes are important (as it is broken down through the liver) and monitoring body weight, as the medication may increase weight. Risperdal may also cause breast milk release and decreased menstruation as well as increased blood sugar and cholesterol/triglycerides.

2. Abilify (aripiprazole): Abilify may cause slightly less weight gain, increased blood sugar or lipids. Abilify does not increase prolactin and will not affect menses/puberty. Abilify has been FDA approved for treating aggression in autism spectrum age 6 and above. The dose range in children is typically between 2 and 10 mg. a day (10 to 30 mg. in adults). It does not typically cause fatigue or sedation. Indeed Abilify may cause an increase in energy, restlessness and gastrointestinal discomfort. It has been shown to be effective in various thought disorders, bipolar disorder and may be a second line in treating aggression in autism spectrum when there are concerns about weight gain.

3. Seroquel (quetiapine): This medication has a wide dose range in adults from 150 mg. per day to 750 mg. per day. Use in children and adolescents is very limited though some adolescent studies have used Seroquel with doses of 25 mg. once or twice daily with slow increases. Seroquel may cause less breast milk production and less decrease of menstruation compared to the other antipsychotic medications. Seroquel has not been shown to be as effective as Risperdal in treating aggression associated with autism spectrum. In adults, it too has been FDA approved for treating Bipolar Disorder.

4. Geodon (ziprasidone): This medication offers a potential advantage over the other second generation antipsychotics in that it tends to cause little or no weight gain, as well as little change in blood sugar or lipids. The dose range is from 20 mg. twice a day in adults up to 80 mg. twice a day A baseline EKG would be helpful as Geodon may increase the QTc interval on the EKG. This may be problematic if the QTc interval approaches or exceeds 450. Geodon may also diminish depressive symptoms as it does, in part, have a mechanism of action similar to antidepressant agents. Careful use in bipolar disorder would seem reasonable as there may be a risk for a slight increase in agitation.

5. Zyprexa (olanzapine): Like Risperdal, this medication has similar uses with a dose range in adults from 5 mg. to 20 mg. per day. In children, Zyprexa may be started at 2.5 or 1.25 mg. per day and adjusted slowly upward. Side effects include sleepiness and weight gain. Because it is broken down by the liver, liver enzyme tests are helpful. Zyprexa is often given at night due to sleepiness and the risk of muscle stiffness is low. The FDA has also approved Zyprexa for the treatment of bipolar disorder (manic depression) in adults. Zyprexa may also increase blood sugar and cholesterol/triglycerides. Zyprexa Zydis melts on the tongue.

6. Clozaril (clozapine): This is the first of the second generation antipsychotics made available in the United States in the late 1980's. Clozaril has been viewed as a breakthrough

medication in the treatment of negative symptoms (lack of motivation, hygiene) along with its effectiveness in treating the positive symptoms (delusions, hallucinations). Not only does Clozaril have minimal risk of tardive dyskinesia but it has also been used as a treatment of tardive dyskinesia in those who develop it. Clozaril does, however, require closer monitoring than other medications which is why it is not a first line treatment. Such follow-up includes regular complete blood counts due to the risk of decreasing the blood count in treated individuals. The dose range of Clozaril in adults is between approximately 200 and 600 mg. per day with higher doses increasing the risk of seizures. In older adults and in the infrequent treatment of younger patients, Clozaril may be started at 12.5 or 25 mg. per day. Other side effects include sleepiness, increased salivation and lowering of blood pressure upon standing. Clozaril has become an important treatment in thought disorders which do not improve with other treatment.

B. First Generation Antipsychotics: These medications were the only widely used treatments in the United States up until the late 1980's for thought disorders, tic disorders and periodic use in autism spectrum. Medications like Haldol and Prolixin are associated with side effects including Parkinsonism (mask-like facial expression, resting hand tremor and shuffling while walking), akathisia (motor restlessness) and dystonia (sudden muscle stiffness of the neck or extremities). Other medications like Mellaril and Thorazine often cause dry mouth, blurred vision, constipation as well as sleepiness and weight gain. Medications such as Trilafon, Loxitane, Navane and Stelazine often cause a combination of such side effects. These medications also carry a risk of tardive dyskinesia (TD) which includes involuntary movements of the mouth, tongue or extremities. TD risk is 4 to 6 percent per year and may not go away in up to 50% of all cases. A treatment of this includes lowering the dose or changing to a second generation antipsychotic and adding vitamin E. Monitoring of tardive dyskinesia can be done with the AIMS (abnormal involuntary movement scale). These medications do treat the positive symptoms (delusions and hallucinations) of the thought disorders but have limited use in the treating the negative symptoms.

F. COMPLIMENTARY ("NATURAL") TREAMENTS

1. <u>Melatonin</u>
Melatonin 0.5 – 1 mg. at 6 p.m. may address delayed sleep phase, a tendency to fall asleep late and arise late the next day. (Often seen in preteens-young adults.)

2. <u>Folic Acid</u>
Folate 1 mg/day – 2 mg/day may augment antidepressant response. This may be considered (for teens/adults) once the dose of the medication is maximized but only a partial improvement in mood is noted.

3. <u>N-Acetylcysteine (NAC)</u>
NAC 600 mg – 1200 mg daily in teens/adults may decrease repetitive hair pulling or other repetitive behaviors. Also, it may augment SSRI's to decrease OCD symptoms.

4. <u>BDNF (Brian Desired Neurotropic Factor)</u>

BDNF is not a treatment per se but is increased in the brain with the use of antidepressants and regular exercise. Hence exercise is mood protective.

G. OVERVIEW - SLEEP DISORDERS IN CHILDREN, ADOLESCENTS AND ADULTS

1. Obstructive Sleep Apnea - Children with OSA may appear fatigued, irritable, distracted, restless and impulsive during the day. Indeed, OSA should be considered in any child presenting with ADHD; crowded airway, snoring and witnessed apneas typically evident. An overnight sleep study is diagnostic and recommendations may include tonsillectomy. Adults with OSA may appear depressed, irritable, inattentive and fatigued.

2. Restless Legs/Periodic Limb Movements in Sleep - RLS is manifested by discomfort while sitting or lying down, particularly later in the day and children/adolescents will report difficulty with leg discomfort. RLS is often associated with PLMS during sleep. With leg jerking movements, the child may shift from deep slow wave sleep to lighter stage 1 or 2 sleep (a micro arousal from sleep). As a result, daytime fatigue, distractibility and difficulty staying in one's seat may be evident. Newer treatments include dopamine agonists. Serotonin reuptake inhibitors may increase RLS/PLMS symptoms. Low ferritin/iron may be a causal factor. Adults may experience RLS/PLMS especially pregnant females with low iron. This may have a genetic basis and run in families.

3. Delayed Sleep Phase - Many children and adolescents have a tendency to fall asleep late and prefer to awaken late the next day. When awakened for school there may be much upset in the home and these children tend to sleep late on weekends. This is a common circadian rhythm pattern addressed by limiting late night light exposure (for example, TV, bedroom light or computer screen) while increasing early morning light exposure (for example, use of a dawn simulator or bedside light on a timer going on one hour before planned wake-up). Other strategies include resetting the sleep/wake schedule either by 15 minutes earlier or progressively later until an appropriate wake/sleep schedule is in place. Melatonin 0.5 to 1 mg. at 6 p.m. may also be helpful in modifying a sleep/wake schedule.

4. Insomnia -Children who have difficulty falling asleep and frequently visit their parents beds may benefit from having two laminated "*Five Minute Passes*" to visit their parents during the night. Over time, just having the passes is reassuring and they may not need to use them. A warm bath or shower just before bed, avoiding anything with caffeine after 12 Noon, scheduling "*Worry Time*" early in the evening, and making use of relaxation strategies all may assist with sleep onset difficulties. For children with Night Terrors, tracking these over several weeks, followed by "*Planned Awakening*" of the child, 15 to 30 minutes before the anticipated Night Terror would occur may break the cycle. Behavioral strategies are the primary approach in addressing insomnia. Adults with insomnia may attempt sleep hygiene, relaxation and sleep restriction.

5. Narcolepsy – This is noted by "sleep attacks" cataplexy (sudden muscle weakness with

emotion, “sleep paralysis” (inability to move as one is falling asleep or arising and hypnagogic hallucinations (also as a person is just falling asleep or arising). Onset is in the late teens but may be overlooked and not diagnosed until adulthood. It may run in families and is treated with medication for alertness (e.g. Provigil/Nuvigil or long-acting Ritalin/Dexedrine).

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