

Early Assessment & Support Alliance Center for Excellence (EASA4E) Medication Guide

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Introduction

For many Early Assessment Support Alliance (EASA) participants, intervention with psychiatric medications is an essential component of recovery. EASA functions as a transdisciplinary team and thus we hope to familiarize all providers in the program with the following: the rationale for medication treatment decisions, general treatment targets, as well as the side-effect profiles for six commonly utilized medication classes (see table 1.)

Table 1: Commonly utilized medication classes.

Medication Class	Description
Antipsychotic	Also known as “neuroleptics,” this group can be broken down into first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). These medications mainly work by blocking dopamine receptors—essentially “turning down the volume” on many psychotic symptoms.
Antidepressant	Includes serotonin reuptake inhibitors (SRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical agents, and tricyclic antidepressants (TCAs). These medications mainly work by increasing neurotransmitter levels and changing the sensitivity of receptors to neurotransmitters, alleviating depression and reducing anxiety.
Mood Stabilizing	Includes medications such as lithium and anticonvulsants like lamotrigine and valproate. These medications largely work by stabilizing neuron membranes to stabilize brain functioning, reducing or preventing manic/psychotic symptoms.
Anxiety Reducing	Include medications that promote sleep (such as zolpidem) as well as medications meant to halt or prevent panic (benzodiazepines such as alprazolam).
Attention and Concentration	Include stimulants (methylphenidate—also known as Ritalin®, mixed amphetamine salts—Adderall®) as well as non-stimulant treatments that promote cognitive arousal (concentration), attention, and wakefulness. These medications may be problematic in the EASA population as they promote increased dopamine transmission—the opposite of antipsychotic medications.
Complementary and Alternative Medicines (CAM)	CAM refers to non-pharmacological interventions—such as mind-body medicine (yoga, mindfulness, acupuncture) that are not traditionally part of Western (allopathic) medicine, here we will specifically talk about natural products (herbs, supplements) which EASA participants may find useful.

We begin with a brief discussion of evidence-based practice and shared decision-making. Next, we provide a case example about an individual with first-episode psychosis (FEP); throughout our discussion of different medications, we attempt to link details to this case example. Of course, every person's course of recovery and medication responses are unique. However, we hope the case example and this guide provide a basic overview, grounding EASA team members with the basics of medication use in our target population—those at risk for psychosis, with attenuated psychotic symptoms, and young people who are currently experiencing psychosis or have had an episode featuring psychosis. Please note that this not a comprehensive guide to all possible psychotropic medications and research, nor does it replace consultation with the clinical team and utilizing sound clinical judgment. We welcome any comments and suggestions for future revisions.

Medical Decision-Making

“It didn’t seem all that special at the time, but the fact that a doctor and I were left alone to figure out what was best for me was a lifesaving miracle.”

-Mark Vonnegut, author of *The Eden Express*, reflecting on the fact that insurance constraints did not impose on collaborating with his psychiatrist.[1]

Psychiatry is a discipline that adheres to evidence-based medicine (EBM) principals [2]. The first of the three principals of EBM is to pay close attention to the best-available research evidence. This usually involves reviewing medical literature using search-engines such as PubMed[3]. For example, if one wanted to determine if risperidone (Risperdal®) was superior to olanzapine (Zyprexa®) for addressing symptoms of psychosis in a teenager, the individual could search PubMed and easily find the Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS) study[4]. This randomized control trial (RCT) showed that risperidone, olanzapine, and molindone (an older medication no longer available) were equally effective at treating symptoms but also demonstrated that there were differences in the side-effect profiles: molindone causing movement problems, olanzapine causing weight gain, and risperidone causing increases in the hormone prolactin. These are important differences that can help inform an EASA participant and psychiatric practitioner which medication would be preferred and inform the team on side-effects to which they should be attentive.

The second principle of EBM is to draw upon clinical experience and exercise sound clinical judgement. High quality psychiatric/mental health practice involves lifelong learning and continuous reflection and reassessment of what might work best, for whom, when, and for how long. Practitioners must respect biases inherent to practice, both in the answers they find in psychiatric research literature and as they draw upon their own clinical experience. As the Pulitzer prize winning oncologist, Siddharta Mukherjee notes[5]: *“The greatest clinicians who I know seem to have a sixth sense for biases. They understand, almost instinctively, when prior bits of scattered knowledge apply to their patients—but, more important, when they don’t apply to their patients.”*

The third principal of EBM is that participants (traditionally called “patients” in medical parlance—likely because being in treatment requires a lot of patience!) fully join in medication/medical decision-making. This respects a person’s or their family’s preferences and the notion that participants are not passive medication-recipients but are active agents in their own care. To this end, it is important to be mindful that everyone’s subjective experience of medication treatment is different. Engaging participants in conversation first about who they are as a person, building a relationship of mutual respect before launching into medication treatment is vital.



Figure 1: Things providers and participants need to talk about.

Understanding the personal context for starting, continuing, switching, or halting medications is important. In the absence of this, practitioners risk failing to learn about potential target symptoms that medications might improve, drivers of symptoms that—if modified or eliminated—would decrease or eliminate the need for medications, and if the participant is taking the prescribed medications and why or why not.

In Table 2 we list five ways in which EASA psychiatrists, nurse practitioners, and other team-members may empower participants to be active agents in their care.

Table 2: Moving from “just a med visit” to a meaningful meeting!

<p>Learn what is important to the participant.</p>	<p>Repeat back what you learned for clarity. For example: “It sounds like what is most important to you is not feeling so tired. Is that right?”</p>
<p>Learn what is important to the participant.</p>	<p>Make explicit when what is most important to the individual sounds or appears different than what their family members, friends, or others feel is most important: “From what I’m hearing, it sounds like your parents are concerned about seeing you angry and frustrated. Would you say that’s right? Or: “Do you agree with your parents point of view? Is this something that you think is important to work on?”</p>
<p>Explicitly invite participants in decision-making.</p>	<p>An example: “Today I would like to talk with you about medications. I would like to share with you what I know, learn what you know about medications, and then make a decision together.”</p>
<p>Present options and provide information on benefits and risks.</p>	<p>Participants need to know about the full array of management strategies - writing this down can be helpful.</p> <p>For example, why would they want to take quetiapine instead of lurasidone? What are the benefits? What side-effects might be more common with one versus the other?</p>
<p>Facilitate deliberation and decision-making.</p>	<p>Let participants know they have time to think things over and ask what else they might need to know to feel confident about their decision(s).</p>
<p>Develop a shared blueprint.</p>	<p>Executive function challenges are something nearly all of us face, but EASA participants may be particularly vulnerable to these.</p> <p>It can be greatly helpful to write down HOW TO:</p> <ul style="list-style-type: none"> •access medications (what pharmacy? how will they pay for this?) •take medications (where will the bottle/pack sit?) •transition (titrate, taper) medications •assess if medications are working (rating scales or simple questions you will pose in the future) <p>Consider typing this up, writing it down and making copies, or sketching this on a dry-erase board and having the participant take a picture of it with their phone.</p>

National Learning Consortium’s Shared Decision Making Fact Sheet. https://www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf
 Published December 2013. Accessed on September 28, 2015.

Case Example

Robby's Story: "Can I Kick It? Yes you can!"
a psychiatric journey of kicking psychosis, side-effects, and rebuilding

Roberto ("Robby") is a 17-year-old eleventh grader at a large suburban high school; he lives with his mother, his mother's partner of five years, along with an older sister (18-years-old) and younger brother (12-years-old.) Roberto enjoys time with friends, listening to "old school hip hop, like Run DMC, Tupac" and has always admired "cool big buildings." He hopes to become an architect and the screen saver on his smartphone features a picture of Frank Gehry's EMP building in Seattle, which he saw on a field trip. To fulfill his dream of becoming an architect, Roberto has felt tremendous pressure in the past to get good grades and earn scholarships.

Roberto entered the Early Assessment and Support Alliance (EASA) after he was briefly hospitalized at a local adolescent psychiatry unit for paranoia; he grew terrified of cameras watching his every move—in his room, on the bus, at school. Roberto's path to the EASA program and into mental health treatment featured a prodromal stretch of several years.

When he was in the fifth grade, at age 11, Roberto's teacher became concerned and sent an email to his mother offering that while he was excellent student, curious with a great vocabulary, Roberto often seemed to struggle with focus. Roberto's mother then met with a pediatrician who had his family and teacher complete some rating scales. When these came back as concerning for attention-deficit/hyperactivity disorder (ADHD), Roberto was started on long-acting methylphenidate (Concerta®.) This "kind of" worked, with Roberto enjoying more focus. Yet, looking back on this, he notes: "that med took away my personality during the day" and "made it so I couldn't sleep at night" and so he stopped it.

Later, when Roberto was in the eighth grade, he started to have anxiety and panic attacks. His mother recalls Roberto "shaking, being totally out of control" before he would get on the bus in the morning. Connecting with a local community mental health center, Roberto worked on a cognitive-behavioral therapy (CBT) workbook with a counselor there. At that time Roberto met with a nurse practitioner at the health center and got started on low dose serotonin-reuptake inhibitor, fluoxetine (Prozac®.) He took this for about two months and as the school-year ended, he quit having anxiety, and so he no longer felt he had need for the medicine. He sheepishly recalls that when he was on fluoxetine he was "not even excited about looking at cute girls anymore," was "maybe a little more restless and angry," and "had some mild headaches when I didn't remember to take my pills."

Roberto has always been committed to completing homework and being one of the best prepared for class, so skipping class or "doing lots of drugs, drinking or whatever has never been what I'm about." Yet,

while at a friend's house last year, he felt comfortable "finally giving weed a try." Roberto reports that he "took a few puffs on a friend's pipe and felt all cool and all relaxed." However, after a few minutes Roberto began to hear his friend's voice, his own, the TV in the next room "echo and go like a dub step: 'wowwa, wowwa'." He felt he could not think clearly. This was on Friday night and he hoped to sleep it off. To this day, though, Roberto feels: "that weed was laced with something," because his symptoms took "a week or two to go completely away." Feeling he heard his name called everywhere he went, Roberto told his mother about what was happening. Together they visited his pediatrician who had just read about a study for those at risk of developing psychosis. "My doctor told me that since my great uncle had schizophrenia (family history of psychosis) and because he was having those weird symptoms after smoking weed (attenuated psychotic symptoms), then maybe I should probably take some fish oil and avoid cannabis." Roberto has been taking omega-3 fatty acid supplements ever since.

One year later, Roberto says that the whispers he heard after the "weed thing happened" resumed. At first he simply heard his name called, but then he heard multiple voices, of men and women—mostly teens—commenting on his actions. "They kept saying 'see, he's not committed. He has no commitment. Watch him closely'." Soon Roberto found cracks in the ceiling in nearly every classroom where he believed cameras were hidden. He felt that people were using their smart phones to report on his whereabouts. Even at home didn't feel safe, with Roberto no longer turning on his computer as he felt the webcam on his laptop was turning on automatically, reporting to an organization he called "The Vision." Approximately six weeks after these symptoms began, Roberto's mother found him sleepless, unshowered, not ready for school, instead cowering in his closet, muttering incoherently about how "The Vision" was terrorizing him. She then took him to a local hospital.

Roberto was evaluated in the Emergency Room (ER), where doctors ran a series of laboratory studies including a toxicology screen. Finding no abnormalities on routine screens, the physicians started Roberto on low-dose aripiprazole (Abilify®) to help reduce his: 1-ideas of reference (seeing holes in the ceiling and believing they held cameras, feeling people's cellphone use meant they were watching him); 2-hallucinations (hearing people comment on his actions); 3-decrease his fearfulness and inability to sleep; and 4-hopefully, overtime, make an impact on his delusions (regarding The Vision monitoring and recording his every move). To combat his anxiety and help Roberto get to sleep, he was also prescribed a benzodiazepine, lorazepam (Ativan®) 1mg. He could also take this during the day if he asked for it—as the emergency physician anticipated Roberto was going to feel very fearful in a busy ER. Roberto waited two anxious days in the emergency department.

By the time Robby went to the adolescent psychiatric unit, it became clear there was a new problem. Roberto felt extremely uneasy, like his "bones were vibrating" wherein he only got relief from this by grinding his teeth and pacing around. The admitting physician realized that Roberto was experiencing akathisia, a side-effect of dopamine-blocking medicine, and thus made the decision to switch Roberto's medicine to risperidone (Risperdal®.) Over the course of hospitalization, this was slowly increased and Roberto's fears, hallucinations, ideas of reference (being preoccupied with "cameras everywhere") all diminished. He began sleeping better as well. Roberto was discharged on risperidone 3mg at night as well as lorazepam 1mg up to three-time-a-day.

Shortly after Roberto got out of the hospital, he met with his EASA medical practitioner. She about learned Roberto's strengths and interests—his artistic skill, ambition to become an architect, his usual easy-going nature, and love of “old school rap.” Roberto and his family also shared his main struggles. He was still having a hard time shaking the notion that people were watching him, not wanting to leave the house and attend school. He also felt dull and tired on the medicine—having lost much of his drive. Roberto and his medical provider then agreed to meet every 2 weeks for 30-45 minutes to talk about his life, if and how he and his family felt the medications were useful, to explore any side-effects he was experiencing, and what they might do to make things better. His medical practitioner believed that combining a supportive psychotherapy approach—one which draws upon Roberto's strengths and his pre-psychotic functioning and keeping these elements in mind for certain moments throughout Roberto's recovery—plus medication management would be key.

In the early course of Roberto's treatment in the EASA program, Roberto's functioning did not improve much. Sure, he reported far less voices, but he was tired, did not want to leave his home, felt his friends were treating him differently. His mother often cried in multi-family group, desperately wishing her son's eager, rosy disposition would return.

Roberto's psychiatrist and the EASA trans-disciplinary team struggled with whether some of Roberto's affective blunting (having a blank, unreactive face) and decreased energy were a side-effect of dopamine-blocking medicine (risperidone), a primary result of changes in the brain due to schizophrenia-spectrum illness (sometimes called negative symptoms), or a result of a post-psychotic depression. When the psychiatrist shared her perspective about these possibilities, Roberto and his family offered that they really wanted to try and reduce the medicine—to see if this would help. During that same visit, Roberto also complained of mild tenderness in his chest and offered: “I'm not very comfortable saying this, but it's like my nipple-area is getting bigger.”

Learning both about Roberto's desire to reduce his medication and about potential side-effects, his doctor drew a blood prolactin level—a hormone which operates in the brain and controls the production of breast tissue and breast milk. The result showed that Roberto's prolactin level was high. So, together Roberto and his doctor decided they would lower his medicine and try a different medicine. In order to help Roberto avoid movement disorders which can come from suddenly discontinuing risperidone (withdrawal dyskinesia), Roberto and his doctor developed a plan to slowly decrease risperidone and to slowly introduce a different antipsychotic, lurasidone (Latuda®.) Of the options Roberto's doctor went over, he particularly liked the idea of lurasidone because he did not want to gain a lot of weight.[6]

At first, Roberto found the change jarring. His voices came back in the form of whispers. Yet, working with his psychiatrist, he had developed a plan for this too: he would wear his headphones and drown out the voices with a new hip hop playlist he'd made—hence doing something interesting (listening to “the classics”—his friends even chipped in for a big iTunes gift certificate so he can play 25 hip hop songs) even amid stress.

Following the change, Roberto's prolactin level returned to normal and he had slightly more energy, but was still found himself feeling "down." Since he had not done well on a serotonin-reuptake inhibitor (fluoxetine) before and the possibility of generating mania, his psychiatrist decided to add the mood stabilizer, lamotrigine. This had to be started slowly to avoid generating what can be a life-threatening rash (Stevens Johnson reaction), but Roberto offered that by this point, he trusted his psychiatrist to help him weigh the pros and cons.

Sure enough, shortly after settling on a regimen that included ziprasidone and lamotrigine, Roberto found himself feeling more balanced and ready to tackle school. Yet now, five months into his treatment, feeling slightly braver to speak honestly, Roberto admitted to his psychiatrist a question that had been nagging at him:

Robby: "Since I'm taking these medications, does that mean you think something's wrong with my brain?"

Doctor: "What do you think Roberto?"

Robby: "No way. That's messed up. I know there were some people watching me. It's like I had a target on my back. I might still."

Doctor: "Well, that reminds me a little of that Tupac song on your playlist: All Eyes on Me."

Robby: "Totally."

Doctor: "I am wondering if you've ever felt in the past if all eyes were on you?"

Robby: "What do you mean?"

Doctor: "I guess I wonder if, even before meds and the hospital and all that, you felt you had to watch yourself very closely?"

Robby: "You know what? Yeah. I did. Like I have always been pretty stressed about school, thinking people are watching my every move."

Doctor: "I wonder if you've felt that too. Like you've got to watch your every move?"

Robby: "Yep."

Doctor: "Well, then, to answer your question about your brain, I wonder if your brain's worry function might be over-active—like you got to the hospital and into the EASA program because your brain's worry function has been WAY more active than it should be. Perhaps medicine's helping tone that down. Does that sound alright?"

Robby: “Think so.”

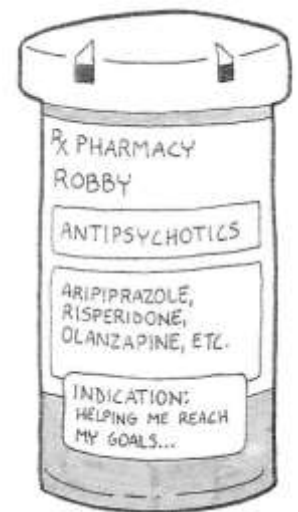
A few visits later, Roberto offered that he was feeling a little bit more at ease, that maybe his mind was playing a trick on him, taking an old worry, about being committed to school—something he’d challenge himself to do, and hearing this message as if it was coming from other people. He said he felt the medicine “might be” helping turn the volume down on this. He also wondered if there might come a day when he could try and completely “down dose” and “get off medicine.”

Roberto’s psychiatrist asked where he would like to be in life, what conditions would need to be in place for him to feel safe doing this and together they made a blueprint to taper and discontinue his medications little by little over the next year. They agreed that if they were not done doing this by the time he left EASA, then she would make sure the blueprint followed him to his next psychiatric provider and that she’d call that person during his first appointment with them or meet with that person alongside him. Robby felt reassured and together they looked at some of his new building idea sketches while listening to a Tribe Called Quest’s “Can I Kick It?”

Antipsychotics

This class of medication is important in treating “positive symptoms.” Positive symptoms include: hallucinations, paranoid delusions, ideas of references (that the television, a movie, or song is speaking directly to a person), extremely disorganized thoughts, and disorganized movements (see Figure 2.) As you might recall from Roberto’s story, antipsychotics (aripiprazole, risperidone, lurasidone) were one of the most important classes of medications on his path to recovery. In this part of the EASA Medication Guide, we will dive deeper into antipsychotics and examine how professionals help participants chose the best treatment for the participant.

Before explaining how antipsychotics work, let us start with where we think positive symptoms come from. Neuroscientists have coined a term, “salience” to describe how our minds assign importance to environmental stimuli.[7] Roberto’s mind assigned excessive importance to the cracks in the ceiling (the stimulus) which led to him to develop an explanation for this increased importance (“salience”) that there were cameras in the ceiling watching him. Roberto hearing “voices” (auditory hallucinations) can also be explained with this model. Hearing voices is not an uncommon phenomenon and considerably more people describe hearing voices compared to the number of people who have schizophrenia.[8-10] Another source of stimuli for hallucinations may be internal monologue - the mind talking to itself. These stimuli are generally accounted for by our minds and cause no distress. However, during psychosis these normal experiences have an inappropriate importance



assigned to them, leading to misinterpretation and often fear. In Roberto's story, he experienced these normal stimuli as an auditory hallucination of real people talking about him or to him.

This assignment of "salience" is thought to be heavily influenced by the neurotransmitter dopamine. Antipsychotics block dopamine transmission between neurons in different areas of the brain, leading to a decrease in the inappropriately assigned importance/salience and a reduction in positive symptoms [11, 12]. The main pathway that is responsible for "positive" symptoms (including hallucinations, ideas of reference, and delusions) is the mesolimbic pathway.

An example of how we see drugs causing psychosis due to overstimulation of pathway occurs when individuals use methamphetamine (e.g. "crystal meth") as this substance causes a rapid increase of dopamine in the brain, often leading to racing thoughts, hypervigilance and paranoia.[13]



Figure 2: "Positive symptoms," the chief target of antipsychotics. Which positive symptoms can you identify in this?

Positive symptoms can be extremely distressing. At times, positive symptoms can lead to individuals doing things that are dangerous and may lead to traumatic outcomes: harm of themselves or others, incarceration, or involuntary hospitalization.[14, 15] This may beg the question, “If antipsychotics are effective at managing the positive symptoms of psychosis, why isn’t everyone who shows signs of psychosis, or is at high risk for developing psychosis, on an antipsychotic?”

1. The symptoms of psychosis may be subtle at first (such as paranoia misinterpreted as anxiety)
2. Some people have full resolution of their symptoms without medications[16-18]
3. Many people who are at high risk do not go on to develop a psychotic disorder[16, 17, 19]
4. The side effects of antipsychotics are significant

As seen in Roberto’s story, side effects play a large part in how participants and their mental health teams choose an antipsychotic medication.

There are two main types of antipsychotics: the first generation or “typical” antipsychotics, and the second generation or “atypical” antipsychotics. Both types of antipsychotics share the primary action of disrupting dopamine's ability to bind to its receptor. There are many differences between the classes, however, the atypical antipsychotics are generally seen as being more tolerable and hence more widely utilized.

Second generation antipsychotic (SGA) medications:

Several large studies have shown no difference between the effectiveness of FGA medications versus SGA medications with respect to reducing positive symptoms in psychosis. Both generations of medications have been shown to significantly reduce the number, frequency, and intensity of the positive symptoms in more than 70% of those who are experiencing psychosis.[20] Many of the second generation antipsychotics have long-acting versions that are injected into muscle, usually in the buttocks or shoulder. These long-acting injectable medications last between 2 weeks and 3 months which may be beneficial for a number of reasons, including: not having to take medications daily, having a ‘steady state’ of medications in the body for long periods of time, and eliminates the possibility of forgetting a dose.[21]

In addition to blocking dopamine, SGA medications also block other receptors, which may be beneficial and/or can cause distressing side effects. Very often clinicians will use the side effect profile to a participant’s advantage. For example, a clinician may use a more sedating medication for participants who have trouble sleeping.

Perhaps the most common and troubling side effects of SGA medications are the metabolic side effects. These medications have the tendency to cause substantial weight gain (10-20+ lbs), elevate lipids and increase blood sugar.[22] These metabolic effects may lead to cardiovascular issues and diabetes. Many participants find the weight gain to be especially problematic, leading them to discontinue the medication. These effects may occur as early as a few days after starting an antipsychotic and are more likely to occur with higher doses and longer duration of treatment. Clinicians need to closely monitor a participant’s

weight, abdominal circumference, lipids, and fasting blood sugar or hemoglobin A1c during the use of SGA medication.

Another group of side effects common to SGA medications are anticholinergic (disrupting transmission of the neurotransmitter acetylcholine) side effects.[23] Recall, SGAs don't only block dopamine, but also other neurotransmitters—like acetylcholine. Blockade of acetylcholine can result in urinary retention, constipation, dry eyes/mouth, and sedation. Interestingly, one of the main problems with antipsychotics and most certainly the first-generation antipsychotics (FGAs) are that they caused movement disorders—some of which can be permanent—involving abnormal writhing movements of the lips, mouth, tongue and extremities. Benadryl® (Diphenhydramine), Cogentin® (benztropine) and Artane® (trihexiphenidyl) are medications with anticholinergic properties that are commonly used to relieve the extrapyramidal symptoms (EPS) commonly caused by FGA medications. Interestingly, the fact that many of the SGA medications have anticholinergic properties may partially explain why they tend to have fewer EPS. Further discussion of EPS continues in the section on FGA medications.

SGA medications can also elevate prolactin—a hormone release by the pituitary gland in the brain.[24] The primary function of prolactin is to induce lactation (production/secretion of breast milk) in women. In excess, prolactin may cause menstrual irregularities, infertility, decreased libido, and gynecomastia in men. If symptoms of hyperprolactinemia do occur, they generally resolve once the SGA medication has been reduced or stopped.

Table 3: Commonly utilized second-generation antipsychotics (SGAs).

Generic	Brand ®	Long Acting Injectable	Sedation	Weight Gain	Notes
Aripiprazole	Abilify Abilify Maintaina	Yes; 4 weeks	+	+	Can be activating
Asenapine	Saphris	No	+++	+++	Tablet 'melts' in the mouth May not eat or drink for 10 minutes after taking
Brexpiprazole	Rexulti	No	+	+	Serotonin and dopamine receptor modulator
Iloperidone	Fanapt	No	+++	+++	
Lurasidone	Latuda	No	+++	Short term: +++ Long term: +	Must be taken with food (min 350 calories)
Olanzapine	Zyprexa	No	++++	++++	
Paliperidone	Invega Invega Sustena Invega Trinza	Yes; 4 weeks 3 months	+++	+++	Active metabolite of risperidone
Quetiapine	Seroquel	No	++++	+++	Sedation dose dependent
Risperidone	Risperdal Risperidal Consta	Yes; 2 weeks	+++	+++	
Ziprasidone	Geodon	No	++	+	Must be taken with food (min 350 calories)

Metformin: what is it and should people on antipsychotics use it?

One of the chief concerns with antipsychotic treatment is that they can generate metabolic syndrome. Metabolic syndrome involves a group of symptoms: elevated blood pressure and heart rate, increased waist circumference, high "bad" cholesterol (low density lipoproteins or LDL) and triglyceride levels, low "good" cholesterol (high density lipoprotein or HDL.) The metabolic syndrome then places people at higher risk for diabetes, heart disease, and stroke.

The EASA Program encourages team members to address these symptoms through encouraging lifestyle modification. This may include formal aerobic exercise programs or simply encouraging people to walk, use a pedometer or smartphone app to gradually increase physical rigor. In addition, some pharmacological treatment may be useful.[25]

Metformin (Glucophage®) is a medicine which is often used for Type II diabetes. Metformin works by decreasing absorption of glucose (sugar) in the intestines, by decrease liver production of glucose, and by increasing the sensitivity of cells to insulin (that's how glucose gets into the target cells that need it for energy). A recent randomized-placebo controlled trial of individuals with first-episode psychosis who were on antipsychotics showed that over six months, metformin reduced LDL, weight and other metabolic parameters[26]. The research team used the following criteria for inclusion in the study, treating individuals if any of these four conditions were met:

- Total Cholesterol >200mg/dL
- Low-density Lipoprotein >130mg/dL
- High-density Lipoprotein <40mg/dL
- Triglycerides >150mg/dL

EASA medical practitioners are advised to keep these parameters in mind, with focus on making sure that if the triglyceride-to-HDL ratio exceeds 3:1, then antipsychotic treatment is altered, lifestyle modifications are encouraged and facilitated, and/or that use of metformin is considered.

Of note, in the study above, participants were given 1000mg of metformin. We recommend starting slightly lower: at 500mg once-a-day with food and then, after one week, moving to either 500mg twice-a-day or 1000mg once-a-day. Again, people who are prescribed metformin should be encouraged to take it with food and they should also be asked about "GI issues." These include nausea, vomiting, stomach pains, gassiness, and diarrhea. The max dose of metformin is 2000mg total per day.

Also, people prescribed metformin should receive regular monitoring, including having their Vitamin B12 (a vitamin that is absorbed in the intestines) checked at baseline and yearly. Finally, people with serious liver, kidney or heart issues should have their psychiatrist/nurse practitioner consult with their primary care physicians before starting metformin[27].

First generation antipsychotic (FGA) medications:

These are the first antipsychotic medications developed and are commonly referred to as "typical antipsychotics" or "neuroleptic" medications. As with SGA medications, FGA medications work by blocking dopamine. Unlike SGA medications, the FGAs features less blockade of other neurotransmitters. Given their high affinity for blocking dopamine receptors in the brain, FGAs can cause significant movement side-effects including akathisia, dystonia, parkinsonism, and tardive dyskinesia. To be clear, both FGAs and SGAs can cause these problems, but FGAs are more likely to cause them. Teams should be vigilant and regularly look for evidence of movement disorder using tools such as the Barnes Akathisia Scale[28] and the Abnormal Involuntary Movement Scale (AIMS.) [29] These two tools can be found in Appendix 7.

Akathisia is an intense feeling of internal restless often described as a feeling of "ants in the pants," one's "bones being on fire," or "internal shaking."

People with akathisia often shift their weight from one to the other, incessantly tap their foot or shake their legs, or have difficulty sitting through a TV program, movie, or class. These symptoms generally occur hours to days after the medication is given but can happen at any time. Akathisia can be treated by lowering the dose of the medication, switching to a different medication (often to a different SGA), or using other medications to treat the akathisia, such as benzodiazepines, beta blockers (such as propranolol), or alpha agents (such as clonidine or guanfacine.)[30] In rare cases, akathisia can be permanent.[31]

Dystonia is an involuntary contraction (or tightening) of a muscle. This can occur with any skeletal muscle, including the muscles that control eye movements. This side effect is particularly dangerous when it involves the muscles used for breathing. Typically, symptoms occur minutes to hours after taking the medication and are most likely to happen early during treatment or after a dose adjustment. However, dystonia can happen anytime the medication is being taken. Treatment is with anticholinergic medication, such as Benadryl® (diphenhydramine) and discontinuing the offending agent is very important.

Parkinsonism is a syndrome where someone without Parkinson's disease experiences stiffening of their muscles, tremor, difficulty walking, and slowed movements—all symptoms of Parkinson's disease. This occurs due to the blockage of dopamine receptors. These symptoms generally occur two weeks to one month after starting an antipsychotic or increasing the dose but can happen at any time. This phenomenon can be treated by lowering the dose of the antipsychotic, switching to a SGA, or using other medications to specifically treat these side effects.[32, 33] Medications commonly used to treat Parkinsonism include benztropine, trihexyphenidyl, and amantadine.[34, 35]

Tardive dyskinesia is a potentially permanent side effect characterized by involuntary and repetitive motor movements. The term "tardive" translates from the French to "late developing" and "dyskinesia" from the Greek, meaning "difficulty moving." These involuntary movements most frequently start with the muscles of the face, but may involve any muscle in the body. Unlike many other side effects, the longer a patient is on the medication, the higher the risk of developing tardive dyskinesia. Also note that young adults and the elderly are at a higher risk of developing this side effect. The most concerning thing about this side effect is that it is often permanent. Early detection is important and all patients on antipsychotics need to be monitored periodically for subtle involuntary motor movements, such as twitches in the mouth or tongue. Treatment of this side effect is complex and often involves medication reduction or switching to another agent.



Figure 3: Concerning antipsychotic-induced movement disorders.

Another important side effect of antipsychotics to be aware of is called neuroleptic malignant syndrome (NMS.) This is rare but is life threatening. Symptoms include confusion, muscle rigidity (usually the whole body), fever, fast breathing, fast heart rate, and increased blood pressure. Participants with these symptoms should immediately be sent to an emergency department for assessment and treatment. It is most likely to occur early during treatment or after a medication adjustment but can occur at any time.

Table 4: Commonly utilized first-generation antipsychotics (FGAs).

Drug Name	Brand ®	Long	Sedation	Weight	Notes
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		Acting Injectable		Gain	
Chlorpromazine	Thorazine	No	++++	+++	Excellent for short-term use, but risk of TD can limit long-term use
Fluphenazine	Prolixin Prolixin Dec	Yes; 2 weeks	++	++	Less sedation and orthostatic hypotension but more EPS risk
Haloperidol	Haldol Haldol Dec	Yes; 4 weeks	++	++	Can be used for tic disorders
Loxapine	Loxitane	No	+++	+	
Perphenazine	Trilafon	No	+++	+++	
Pimozide	Orap	No	++	++	Can be used for tic disorders
Thioridazine	Mellaril	No	+++	+++	Very limited availability
Thiothixene	Navane	No	++	+	
Trifluoperazine	Stelazine	No	+++	+	

Clozapine:

There is only one medication that has been shown in clinical trials to be superior to other antipsychotic agents: clozapine. Unfortunately, clozapine carries with it a significant set of risks. As such, this agent is typically prescribed only to someone suffering from psychosis or schizophrenia who has failed to improve in terms of symptom reduction with two or more medications, when someone has severe symptoms featuring suicidality, or when individuals cannot tolerate other medications due to movement disorders.

Clozapine's effectiveness comes at the cost of potentially life threatening side effects. Clozapine has five Food and Drug Administration (FDA) black box warnings: Agranulocytosis, myocarditis, seizures, orthostatic hypotension, and increased mortality in the elderly with dementia related psychosis. In addition to these potentially life threatening side effects, other side effects including excessive salivation, drowsiness, and weight gain are all common.

Due to these risks, clozapine is a highly-regulated medication. To obtain this medication from the pharmacy, the pharmacist must receive weekly laboratory reports showing that there has been no drop in white blood cells. After six months, these blood tests can be moved to every two weeks, and after one

year, blood work can be every month for the duration of someone's Clozapine treatment.[36] If there is ever a drop in white blood cells, then treatment modifications must be made. Of note, agranulocytosis typically occurs early during treatment, but can happen at any point.

Due to the risk of seizures, clozapine is started at a very low dose and must be increased slowly. Myocarditis can happen at any time, as can orthostatic hypotension. Even with all these serious side effects, clozapine can be a life changing medication. It is the only medication that has been found to decrease suicidality in schizophrenia, and it also does not cause movement disorders and in fact is considered a treatment for tardive dyskinesia, so it can be used in patients who cannot tolerate other antipsychotics due to those side effects.

Table 5: A class of its own—Clozapine.

Drug Name	Brand ®	Long Acting Injectable	Sedation	Weight Gain	Notes
Clozapine	Clozaril	No	++++	++++	Proven to reduce suicides in schizophrenia Drooling can be an issue

A note on the newest FDA approved medications

As new medications are available, many people—both EASA participants and clinicians—may be tempted by medication debuts in the medical literature or flashy TV or internet ads, to assume that “newer is better.” However, it is important to note that this is not necessarily true. The primary mandate for drug approval by the Food and Drug Administration (FDA) involves determining safety and efficacy, not superiority to currently available medications. Therefore, it is important to review the evidence from trials of new medications. As newer medications have been studied in fewer and often shorter-term trials, it typically takes time for the field to evaluate common side effects and how well people tolerate newer medications. Below we offer some thoughts about the newest second-generation antipsychotics.

There have been a fair number of recent trials involving asenapine (Saphris®), iloperidone (Fanapt®), and lurasidone (Latuda®). Literature review has many expected results, with some notable comparisons to other second-generation antipsychotics. Side effects for each medication are dose-dependent (the higher the dose, the more side-effects one experiences); with one study citing evidence of doses less than 120mg of lurasidone being better tolerated among children and younger adolescents. Overall, the side effects are similar to that of other second-generation antipsychotics. When looking at elevations of prolactin (which can lead to breast development in males or breast milk production), a comprehensive review of studies suggests that asenapine and iloperidone are similar to clozapine, with lurasidone having a lower impact similar to ziprasidone and olanzapine. In terms of short-term (≤ 12 weeks duration) weight gain and risk of the metabolic syndrome, iloperidone (+2.50kg), asenapine (+1.16kg), and lurasidone (+0.49kg) showed significant increases. For short-term changes, iloperidone showed increases in total, good (HDL), and bad cholesterol (LDL, VLDL) (Total Cholesterol: +11.60mg/dL; HDL: +3.6mg/dL; LDL: +10.30mg/dL); lurasidone had a mild increase in good cholesterol (HDL: +1.50mg/dL).

Meanwhile, asenapine had an increase of 6.53mg/dL in total cholesterol during longer term trials.[6, 37, 38]

Brexipiprazole (Rexulti®) is a new second-generation antipsychotic that is a serotonin-dopamine receptor modulator. In this sense, it is like aripiprazole, which is effective as an antipsychotic and an adjunctive treatment for depression. Studies thus far have compared the medication to placebo and have shown it is effective as an adjunctive treatment for major depressive disorder (MDD)[39]; especially those patients with sleep disturbance[40]. One study showed that adjunctive treatment with brexpiprazole for major depressive disorder led to an improvement in sleep and daytime awareness[41]. A small study published late in 2016 suggested that it is effective in early-episode schizophrenia in adults, with the most common side effects being sleep disturbances, weight gain, and nausea[42]. There have not been studies specifically in children and adolescents.

Antidepressant Medications

Antidepressant medications encompass a variety of medications that are used in the treatment of mood and anxiety disorders. These medications may also be helpful for anger, impulsivity, and eating disorders. For those with a personal or family history of bipolar disorder, these medications can precipitate manic symptoms when used in the absence of a mood-stabilizing medication[43]. Antidepressant medications are thought to work by effecting specific neurotransmitters in the brain, typically serotonin, norepinephrine, or a combination of the two. To see clinical effects, these medications must be taken daily and have a period of two to six weeks to reach full effect at a given dose.

These medications are typically started at a low dose and are gradually increased as tolerated. Many side effects are temporary but can be uncomfortable, such as nausea and headaches. Other side effects, such as increased sweating, can be quite distressing although not dangerous. Stopping these medications abruptly can result in a discontinuation syndrome[44], symptoms of which include dizziness, nausea, vomiting, diarrhea, and headache. This can be quite uncomfortable but is not life threatening and will resolve within a few days.



There are three fundamental concerns with prescribing/taking antidepressant for treating depression. First, some of the antidepressants, particularly older generation medications including tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can be lethal in overdose—worrisome for individuals who might be taking an antidepressant due, in part, to suicidality.

Another potentially fatal concern with antidepressants is a condition called serotonin syndrome[45]. Serotonin syndrome involves over-excitation of the brain resulting in anxiety, agitation, sweating, elevated heart rate, increased blood pressure, increased body temperature, tremor, and muscle stiffness. It commonly occurs when multiple medications that effect serotonin levels are taken at once or in overdoses of antidepressant medications. This can also occur with use of

recreational substances (ecstasy or MDMA, cocaine) that also impact serotonin[46, 47]. It is important to be aware of these symptoms in participants starting antidepressant medications, particularly if they take other medications or use recreational drugs.

Finally, it should be noted that all antidepressant medications carry an FDA black box warning for increased suicidal thinking and behavior in individuals less than 25 years old. It is important to note that this was reflective of a small number of study participants who experienced suicidal thinking[48] (4% in the active drug group, and 2% in the placebo group.) *Importantly, there were **no** increases in suicide attempts or completed suicides amongst the more than 100,000 children and adolescents involved in the studies that lead to this black box warning[48].*

These medications are typically used for a period of months (usually nine to 12) once symptoms have resolved, after which the dose is slowly lowered until the medication can be safely stopped. Some participants and providers prefer to continue these medications to avoid or prolong the time between future episodes. Presently, there are no known negative side effects for remaining on these medications long term. Discussing the risks and benefits of long-term use are best made collaboratively between the participant and their provider.

In the case study, Roberto develops symptoms of an anxiety disorder as a teenager. After initial psychotherapy/counseling is ineffective at resolving his symptoms, his provider starts Roberto on fluoxetine, an antidepressant medication. One would expect full effect with good adherence after four to six weeks, and Roberto had full resolution of his anxiety within two months. Roberto did experience some common side-effects including: decreased libido, increased restlessness/anger, and mild headache. These side effects may have improved with time, or his provider could have tried a lowered dose or switched to a different medication. Roberto self-discontinues this medication, luckily without any discontinuation symptoms.

Brief Description of the Most Commonly Used Medications by Class

Selective Serotonin Reuptake Inhibitors (SSRIs or SRIs)

These are often first medication used for depression and anxiety as they typically work well and generally have fewer side effects than other types of antidepressants[49]. Side effects are common in the first weeks of treatment and with dose increases. The most common side effects are gastrointestinal (i.e. nausea, diarrhea, constipation) and headache. Some medications can cause an adverse effect known as activation[50] (i.e. restlessness, hyperactivity, and/or agitation) while others can cause sedation. In some participants, these medications can lead to decreased libido, difficulty with maintaining sexual arousal, and delayed or absent orgasm. These medications can affect the metabolism of other medications. It is very rare that overdoses of these medications are life threatening.

Table 6: Commonly utilized serotonin-reuptake inhibitors (SRIs).

Generic	Brand ®	Activating or Sedating	Drug-drug interactions	Notes
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Citalopram	Celexa	More sedating	++	May cause heart rhythm problem in some
Escitalopram	Lexapro		+	“Cleaned up” version of citalopram
Fluoxetine	Prozac	More activating	+	Lasts 5 days; low risk of discontinuation syndrome
Fluvoxamine	Luvox		+++	More drug-to-drug interactions
Paroxetine	Paxil Pexeva Brisdelle	More sedating	+++	Lasts 23-25 hours; high risk of discontinuation syndrome
Sertraline	Zoloft	More activating	+	May need twice a day dosing in adolescents

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs are typically tried when SRIs have not been effective or when there are coexisting medical conditions (such as chronic pain.)[49] These medications can be more difficult to tolerate initially, as they are more likely to cause activation[50] (i.e. restlessness, hyperactivity, and/or agitation), but overall tend to have very similar side effects to SRIs.

Table 7: Commonly utilized serotonin-norepinephrine reuptake inhibitors (SNRIs).

Generic	Brand ®	Notes
Desvenlafaxine	Pristiq	“Cleaned up” venlafaxine Can be difficult to stop due to discontinuation syndrome
Duloxetine	Cymbalta	Not to be used in participants with kidney disease Can be helpful for chronic pain
Levomilnacipran	Fetzima	May improve cognition in depressed participants
Venlafaxine	Effexor	Can be difficult to stop due to discontinuation syndrome

Tricyclic Antidepressants (TCAs)

TCAs are older, less commonly used antidepressants as they have more side-effects and are be lethal in overdose[49]. They are often used for other conditions, such as chronic pain, chronic headache, and insomnia.

Common TCAs: amitriptyline, clomipramine, doxepin, imipramine, nortriptyline

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs are the oldest class of antidepressants. They have the most side effects and require a strict diet due to a potentially lethal interaction with certain foods[49]. There are many serious and potentially lethal interactions with other medications, including over the counter medications (such as cold medicine.)

Common MAOIs: isocarboxazid, phenelzine, selegiline

Atypical Antidepressant Medications

There are antidepressant medications that do not fit into any of the above classes. They have different ways of affecting neurotransmitters including serotonin, norepinephrine, and/or dopamine.

Table 8: Commonly utilized “novel antidepressants.”

Generic	Brand ®	Unique Features
Bupropion	Wellbutrin Wellbutrin SR Wellbutrin XL Forfivo Zyban	May also affect dopamine (along with serotonin) May increase risk of seizures Can increase anxiety May decrease appetite Can be used for smoking cessation, inattention Can be added to SRIs to reduce sexual side effects
Buspirone	Buspar	Typically used for anxiety disorders
Mirtazapine	Remeron	Sedating and appetite stimulating at low doses; this decreases with higher doses
Trazodone	Desyrel	Often used as a sleep aid
Vilazodone	Viibryd	May have fewer sexual side effects
Vortioxetine	Trintellix	May improve cognition in depression

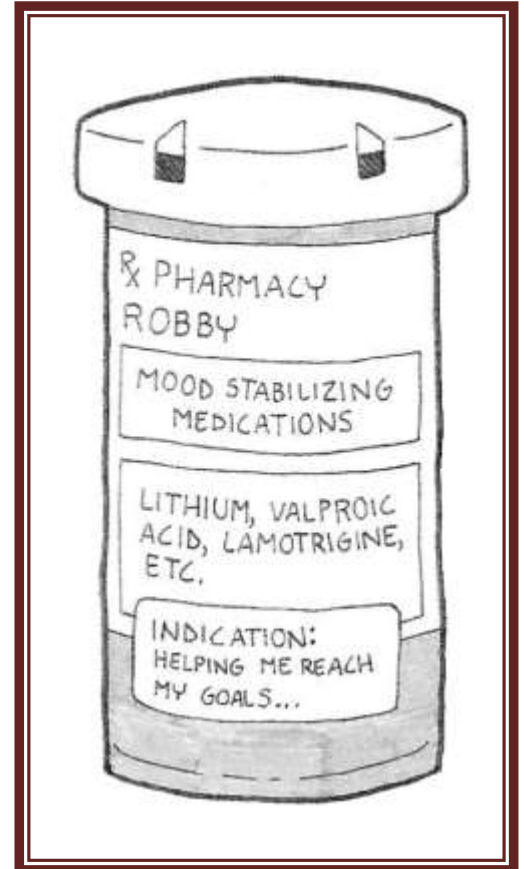
Mood Stabilizers: Lithium and Antiepileptic Medications

In this section, we will explore “mood stabilizers,” a group of medications that includes lithium and a handful of antiepileptic (drugs used to prevent seizures) medications. These medications are thought to

work by "stabilizing" neurons in the brain that fire too rapidly, causing imbalances in mood. The clinical effects are seen with a reduction or complete absence of seizures, and in the case of mood disorders, a decrease of manic or hypomanic symptoms.

Bipolar, or cyclic, mood disorders are characterized by the "highs" of mania, and "lows" of depression which individuals "cycle" through. Symptoms of mania include having distinctly angry or abundantly joyful, bubbly and triumphant mood. Along with this, one may have little or no need for sleep, become grandiose, impulsive, take risks or seek pleasures outside what they would normally deem appropriate, start a lot of projects, grow distractible, speak loudly and rapidly[51]. While many participants may have one or two of those symptoms regularly, a manic episode is diagnosed when multiple symptoms have been occurring every day for at least a week and if/when the symptoms cause profound functional impairment (usually to the point of needing hospitalization.) A hypomanic episode is different. These are less intense with symptoms lasting less than a week. Mixed episodes are periods of time when a participant meets both the criteria for a manic or hypomanic episode and a depressive episode[51].

Mood stabilizers are primarily indicated in bipolar disorders; however, they are often used as adjunctive treatments in psychotic and unipolar depression. There is currently no evidence that any of these medications are effective as a primary treatment for psychotic disorders[52-56]. Although these medications have been studied in children and adolescents as anti-seizure treatments, these medications only have FDA indications in adults for mood disorders. Even if a participant has not been diagnosed with a bipolar or seizure disorder, these medications can be helpful for several symptoms, such as impulsivity, irritability, chronic headaches, and morbidity from suicide.



Participants may not benefit from these medications if there are no clear indications of a bipolar or depressive disorder. Additionally, participants with liver, thyroid, or kidney disease may not be able to take these medications without increased monitoring as they are at increased risk for significant adverse effects. Participants who have difficulties in adhering to a medication regimen may struggle to receive appreciable benefits from these medications as they often require achieving and maintaining a steady level in the bloodstream.

When someone is prescribed these medicines, they need to be regularly monitored for side-effects and many times will need to have their blood drawn. Monitoring can include obtaining level of medication in a participant's blood, complete blood cell counts, liver/kidney/thyroid functioning, and presence of other symptoms such as rash, confusion, tremor, or tinnitus (ringing in the ears.)

Lithium (Lithobid®, Eskalith®)

Lithium has historically been the "gold standard" for treating manic episodes[57]. It is also commonly used as a maintenance medication to reduce the frequency of manic episodes in individuals diagnosed with bipolar disorder. It is also used in depression, as it has excellent evidence for decreasing suicide in individuals with mood disorders[58]. Unfortunately, there is no evidence that lithium also decreases suicides in individuals with psychotic disorders[53].

Lithium has some very common side effects. When starting lithium, nausea and a tremor in the hands is common. With long term use, lithium can cause changes in kidney and thyroid functioning. Individuals with thyroid or kidney disease can still take lithium, but with much more intense monitoring. Lithium is a salt, so maintaining consistent hydration is very important. Drinking too much fluid can cause low levels of lithium and sodium in the body, increasing the risk of seizure due to low sodium levels. Dehydration can cause lithium levels to quickly become toxic. Lithium toxicity can be life threatening, but it can also be treated if recognized. Common signs of toxicity include ringing in the ears, unsteady gait, and confusion. Because many common medications can interact with lithium (such as ibuprofen), lithium requires careful and frequent monitoring with blood draws.

It is important for those taking lithium to keep a consistent balance of fluids and salts. For those who are active, this means paying careful attention to replacing fluids and electrolytes when playing or working (especially with high temperatures or profuse sweating.) Tylenol® should be used rather than ibuprofen containing pain relief or for fevers.

Antiepileptics

As noted above, many antiepileptic medicines not only treat seizures but also seem to impact mood. While each of the antiepileptics has a unique side-effect profile, there are some prescribing principles for this class. First, all antiepileptics need to be titrated to effective doses. Also, there is a risk of seizures with abruptly stopping these medications, even in individuals who do not have epilepsy. Many of these medications require frequent monitoring with blood draws due to effects on the liver and bone marrow. Only three antiepileptics have been specifically studied and shown to be useful in bipolar disorder, but others are commonly used "off label"—meaning they do not have FDA approval, but are still used as conventional wisdom suggests they may be beneficial. Some of these medications may have additional benefits in treating irritability and impulsivity (divalproex and lamotrigine), migraine prevention (divalproex and topiramate), and alcohol use (topiramate.)

Of note, a major concern with psychiatric medications in general and with many mood stabilizers in specific are their association with birth defects. Before starting/changing medications, discussions about the potential for pregnancy, the risks of becoming pregnant while on a given psychiatric medication, and how to reduce those risks is imperative. For up-to-date discussions on the risks of taking different psychiatric medications during pregnancy and while breast feeding, we urge readers to look at outside resources such as <https://womensmentalhealth.org> and to seek consultation.

Lamotrigine (Lamictal®):

Lamotrigine is a very well tolerated medication that may be helpful in participants who have not responded well to SRIs for depression[59], as was the case for Roberto in the case example. Lamotrigine has a very serious risk of a life-threatening rash if the dose is increased too quickly. This rash, called Stevens Johnson Syndrome, typically starts in the mouth (mucosal surfaces) before moving over the entire body. The rash is life-threatening as the skin blisters and fills with blood. The medication is stopped immediately at the first sign of any concerning skin changes. There is a high frequency of non-life-threatening skin rashes, but out of an abundance of caution lamotrigine is typically stopped with any rash. It typically takes six to eight weeks for a participant to get to a therapeutic dose of lamotrigine. Once on a therapeutic dose, there are relatively few side effects and no required laboratory studies or specific monitoring.

Valproic acid (Depakene®) /valproate (Depacon®) / divalproex (Depakote®):

These are all the same medication – they only differ by formulation and the length of time the medication takes to be processed in the body (dosed multiple times or once per day.) Divalproex is most commonly used, as it is a medication that can be taken by mouth and can be dosed once daily. Divalproex is primarily indicated for acute and mixed mania, although it also has an indication for migraine prevention. It is also commonly used for irritability and impulsivity. Divalproex has several common side effects including sedation and weight gain. Serious side effects include liver failure, pancreatitis (inflammation of the pancreas), and lowering of the body's ability to produce platelets. Divalproex should be used with caution in young women as it is associated with polycystic ovarian syndrome (PCOS) and with birth defects.

Carbamazepine (Tegretol®), oxcarbamazepine (Trileptal®), topiramate (Topamax®):

In individuals who have not found benefit with the above medications, trial of one of these may be beneficial. Only one formulation of carbamazepine, Equetro®, has shown in studies to effectively treat acute mania and mixed episodes. Both carbamazepine and oxcarbamazepine can cause low sodium levels and decrease the production of blood cells in the bone marrow. Individuals of Asian (including south Asian Indian) heritage are at an increased risk of a life-threatening skin reaction, and typically should not take this medication if possible. Topiramate has been studied in treating individuals with addiction to alcohol and has shown some mixed success. Individuals with severe migraine headaches may find it helpful. It frequently causes individuals to endorse a feeling of "brain numbing" or difficulty thinking—earning the unfortunate nickname "Dopamax." Based on evidence from several studies, Topiramate is occasionally used alongside antipsychotic medication to help reduce weight gain and decrease appetite[56].

Antianxiety and Sedative Hypnotic Medications

Anxiety is a very common experience, and there is a high prevalence of anxiety disorders in the general population[60]. It is not uncommon for young adults with attenuated psychotic symptoms to experience anxiety or have a co-occurring anxiety disorder and anxiety may be an initial presenting complaint of a

person who develops psychosis as the internal running negative thoughts of anxiety disorders have overlap with auditory hallucinations (see Figure 2.)



Figure 4: “Robby” overwhelmed at school.

Anxiety disorders often first present in adolescence and early adulthood. Anxiety and psychotic symptoms may overlap and be difficult to differentiate for some participants.

Anxiety takes many forms and presents in several ways. It can be a specific fear of an object (spiders) or situation (heights.) It can occur as panic, which is when the mind reacts as if it is in danger, or goes into “fight, flight, or freeze” mode with no actual danger present. It can manifest as chronic and unrelenting worry about multiple issues. There are many physical sensations caused by anxiety, such as muscle tension, fatigue, headaches, elevated heart rate, shortness of breath, numbness and tingling in their extremities, dizziness, sweating, nausea and/or ringing in their ears.[61]

Most anxiety disorders are treated with a combination of psychotherapy and SRI or SNRI medications. Unfortunately, these medications can take several weeks to get to a therapeutic level and offer relief. Sometimes a provider will prescribe a medication that acts more quickly to relieve anxiety and/or to promote restful sleep. These medications come from multiple classes, including benzodiazepines, atypical antidepressants, sedative hypnotics, antihistamines, and antihypertensive medications.

Benzodiazepines

Benzodiazepines are effective for the short term treatment of some types of anxiety such as panic attacks[62]; however for other types of anxiety (generalized anxiety or social phobia), they are not generally considered first line agents. The main treatment for these types of anxiety is a combination of either SRIs or SNRIs and Cognitive behavioral therapy.

Benzodiazepines act on the brain in a very similar way to alcohol. All benzodiazepines work in the same way, but are effective for short (1-2 hours), moderate (4-6hours), or long (8-12 hours) periods of time. Significant side effects can include developing dependence (physiological and/or psychological), confusion, balance problems, difficulty walking, and others.[62] Benzodiazepines can be fatal in

overdose[63]. In participants taking narcotics or using alcohol, the risk of accidental overdose and death is even greater.[64]

Benzodiazepines are a controlled substance, meaning that they have special prescribing guidelines. They can be misused and/or abused, and are bought, sold, shared or traded outside of the medical system. Extended use of benzodiazepines often results in physiological dependence; in these cases, stopping the medication “cold turkey” can result in seizures or death. Participants should not stop taking a benzodiazepine suddenly but should work with a prescriber to taper off the medication slowly.[62]



There are two main controversies with using these medications. First, benzodiazepine use can lead to physiological and psychological dependence. People may find themselves needing increasing doses to get the desired effect. Additionally, in helping provide a sense of calm, benzodiazepines can also give someone a sense of intoxication or disinhibition, which may lead to misuse. Another concern that remains on the mind of practitioners is data suggesting a link between an increased risk of developing dementia later in life and exposure to benzodiazepines. However, there are conflicting studies regarding this; consequently, many practitioners and patient feel it is appropriate to prescribe/utilize benzodiazepines on a short-term basis to curb anxiety and promote sleep.[65, 66].

Common medications include, from short to long acting: Alprazolam (Xanax®), lorazepam (Ativan®), diazepam (Valium®), clonazepam (Klonopin®.)

Antihistamines

Antihistamines are medications which block histamine receptors. There are three types of histamine receptors in the body. The histamine system helps regulate immune response (think allergies), hunger, and sedation. There are two antihistamines which are typically used for their sedative effects: Diphenhydramine (Benadryl®) and hydroxyzine (Atarax® or Vistaril®.) These medications lose effectiveness over time (typically 2 weeks of consistent use) but can be helpful for sleep initiation and temporary reduction in anxiety.

Antihypertensive Medications

Medications that reduce blood pressure or keep the heart from beating faster can be useful for anxiety. Propranolol (Inderal®) is commonly used for people who have anxiety related to performances[67], such as giving a speech. Clonidine (Catapres®/Kapvay®) and guanfacine (Tenex®/Intuniv®) are two medications which are often used for hyperactivity and can also be sedating.

Melatonin

Melatonin is a hormone the brain releases to regulate the sleep-wake cycle. It is offered as an over the counter supplement. It can be helpful for treating sleep problems due to delayed sleep phase[68], but may not be as effective in other types of insomnia.

Sedative hypnotics

This group of medications includes zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®.) These medications are used for sleep initiation and maintenance and share some of the pharmacological characteristics of benzodiazepines. They differ from benzodiazepines because they bind very selectively to certain receptors. They largely differ by how long they act on the brain. Some common side effects include headaches and dizziness. Sometimes medications in this group can lead individuals to do complex tasks when they are asleep including eating, driving, and making phone calls.[69] Some people experience decreased alertness the next day

It is important to note that women metabolize zolpidem (one of the medications in this group) at a reduced rate compared to men and thus should use lower doses of the medication.

Atypical antidepressant Medications

There are two atypical antidepressant medications which are commonly used for sleep: trazodone (Desryl®) and mirtazapine (Remeron®.) Trazodone carries the risk of priapism, which is an erection of penile or clitoral tissues lasting more than four hours. While priapism can happen in both men and women, there have been relatively few reported cases in total and of those, fewer reported cases in women than in men. Mirtazapine is very sedating at low doses, but loses this effect as the dose is increased. It also is well known to cause increased hunger and thus should be used with caution alongside second-generation antipsychotics—as one would then be on two medications apt to increase appetite/promote weight gain.

Attention-Deficit/Hyperactivity Disorder Medications

Many symptoms overlap between Attention-Deficit/Hyperactivity Disorder (ADHD) and the cognitive dysfunctions in psychotic disorders—which are also called “negative symptoms,” see Figure 3. Inattention, impulsivity, and low frustration tolerance can occur in both ADHD and psychotic states[70]. Other symptoms of ADHD include forgetting routines and items, frequently losing things, hyperactivity, being easily distracted, getting lost in thoughts or daydreams, and others. There are also medical reasons to consider as causes for poor attention and hyperactivity such as poor sleep, obstructive sleep apnea, iron deficiency, thyroid dysfunction, and vitamin deficiencies.



Figure 5: Negative symptoms of psychosis. Which symptoms can you identify in these panels?

If difficulties with attention started early in life, typically before age 12, it is more likely that ADHD is a valid diagnosis[71]. If symptoms start around the same time as psychotic symptoms begin, making the diagnosis is much more difficult. Roberto's case demonstrates this complexity. Attributing Roberto's difficulty with focus in the fifth grade to ADHD was reasonable. It is also possible that this difficulty with focus was related to the prodromal phases of his psychotic disorder, especially it had not been noticed earlier in his education. An additional possibility is that he has both ADHD and a psychotic disorder.

Stimulant medications (methylphenidate and mixed amphetamine salts) have proven to be the most effective treatment for inattention in ADHD[72]. They are available in short (3-5 hours), intermediate (4-8 hours), and long-acting (8-12 hours) formulations. Both amphetamine salts and methylphenidate preparations block the reuptake of dopamine and norepinephrine. Amphetamine salts also increase

release of both these neurotransmitters. These neurotransmitters are important for many brain functions, including attention and motivation.

Table 9: Commonly utilized stimulant preparations.

Class	Brand ®	Duration of Effect	Notes
Methylphenidate	Ritalin	Short acting	May be sprinkled on food Must be swallowed whole Chewable or liquid May be sprinkled on food Must be swallowed whole Liquid Chewable Must be swallowed whole Transdermal patch
	Ritalin LA	Intermediate	
	Ritalin SR	Long acting	
	Methylin	Short acting	
	Metadate CD	Intermediate	
	Metadate ER	Long acting	
	Quillivant	Long acting	
	Aptensio XR	Long acting	
	Concerta	Long acting	
	Daytrana	Long acting	
Dexmethylphenidate	Focalin	Short acting	May be sprinkled on food
	Focalin XR	Long acting	
Mixed amphetamine salts	Adderall	Short acting	May be sprinkled on food Must be swallowed whole
	Adderall XR	Long acting	
	Dextrostat	Short acting	
	Dynavel XR	Long acting	
	Eekeo	Short acting	
Amphetamine isomers	Dexedrine Spansules	Long acting	Must be swallowed whole Liquid Must be swallowed whole
	ProCentra	Short acting	
	Vyvanse	Long acting	
	Zenzedi	Short acting	

Common side effects of stimulant medications include appetite suppression, weight loss, insomnia, headache, and irritability. In individuals with a history of heart problems, stimulant medications can cause irregular heart beat and other issues[72]. These medications can also be misused, especially in the young adult population. Studies indicate there is a lower likelihood of misuse in long-acting stimulants[73].

Albeit rare, another potential side effect of stimulant medications is psychotic symptomology due to their potential for increasing dopamine signaling. Studies initially estimated that this side effect occurs in 0.25-1.5% treated with stimulants[74, 75]. However, these studies may not have been representative of the complexities real-world clinical populations and thus underestimated the risk. A recent study considered some of these complexities by investigating the association between stimulant use and psychotic symptoms (hallucinations, delusions, abnormalities in perception) in children of parents with major mood and psychotic disorders. A significant association between stimulant use and development of psychotic symptoms in children of parents with mood or psychotic disorders was found[76]. Although further research is needed to clarify some details, this study supports considering family history of a mood or psychotic disorder as a risk factor for development of psychotic symptoms when prescribed a stimulant.

There are several other, non-stimulant medications which are commonly used to treat ADHD. One of these medications is atomoxetine (Strattera®.) It is a selective norepinephrine reuptake inhibitor. Effects can be seen after one week but greatest effects may not be seen until after six weeks. Side effects include nausea and headache. There is less risk of causing or worsening psychosis and little to no abuse potential. Also, it may have less pronounced effects on appetite and sleep than stimulants. Other medications in the antidepressant class which are used in ADHD include bupropion (Wellbutrin®) and two tricyclic antidepressants: imipramine (Tofranil®) and nortriptyline (Pamelor®/Aventil®.) There is some evidence for the effectiveness of these non-FDA approved ADHD treatments, which is comparable to that of behavior therapy, but less than stimulants and atomoxetine[72].



Two other medications, clonidine (Catapres®/Kapvay®) and guanfacine (Tenex®/Intuniv®) are also labeled for use in ADHD, both with or without stimulants. There are also several non-FDA approved medications that are sometimes used in the treatment of ADHD. Of note, small reports show some support for clonidine helping improve psychotic symptoms[77]. These medications generally do not worsen psychotic symptoms.

In summary, there are both risks and benefits to using medications for ADHD treatment in participants with psychosis. There have not been many studies done to clearly guide treatment of these two conditions together. Nonetheless, there is some research and principles that do provide guidance. At the right dose, research suggests that stimulants and antipsychotics can be safely used together and may in fact work in a synergistic fashion[78]. However, the risk of worsening psychosis by adding a stimulant to an antipsychotic medication, as discussed above, still exists. Current literature suggests treating the psychosis first[79]. If symptoms of ADHD persist after psychotic symptoms are well-controlled, less-risky non-stimulant treatment options for ADHD should first be considered, such as atomoxetine, bupropion, and non-medication options (education and behavioral interventions.) If ADHD symptoms are still

problematic after a non-stimulant trial, a stimulant trial can be considered with close monitoring, after discussion with the participant along with his/her support system.

Complementary and Alternative Medicine

Complementary and Alternative Medicine, or CAM, involves the use of diagnostic tools, nonpharmacological interventions, and medical treatments which complement allopathic medicine. CAM covers a heterogeneous spectrum of ancient to new-age approaches aimed at preventing or treating disease[80]. Participants may turn to CAM due to a preference for holistically focused treatment or due to difficulty tolerating or gaining sufficient relief with their current treatments. It is estimated that over one third of adults use some type of CAM, with this number projected to continue increasing[81]. The FDA does not currently approve the use of alternative medications or supplements. While a full review of CAM for psychosis is beyond the scope of the EASA Medication Guide, we did wish to mention three treatments frequently discussed in the Oregon treatment community: Omega 3 polyunsaturated fatty acids, L-theanine, and zinc.

Omega 3 polyunsaturated fatty acids (PUFA)

Polyunsaturated fatty acids (PUFAs) are the building blocks of cell membranes. Omega 3 fatty acids play a key role in healthy neurodevelopment. Individuals with a psychotic disorder have a lower concentration of omega 3 PUFA in their brain. Early research signaled that omega 3 supplementation may prevent or delay the onset of psychosis in individuals at ultra-high risk for a psychotic disorder[82], however, a follow up study did not confirm this to be true[83]. That is why, in the case example, when Roberto was having early warning signs of psychosis, his primary care physician suggestion PUFA or omega 3 treatment. The body cannot make enough of these fatty acids, so one must get them through either diet (fish and vegetable oils) or supplementation. Omega 3 polyunsaturated fatty acids are used as prophylactic treatment for children, adolescents, and young adults at elevated risk for psychosis.



Table 10: Polyunsaturated Fatty Acids (PUFAs)

Common Dosing	Safety/Monitoring	Adverse Effects
1.2 grams per day by mouth of omega 3 supplement containing: - 700 mg eicosapentaenoic acid	Supplements derived from fish may contain mercury and other contaminants. FDA recommends consuming a variety of fish species to minimize contaminant exposure. FDA has information	GI - nausea, indigestion, fishy eructation, loose stools/diarrhea Hematologic - prolongs bleeding time but no clinically

<p>(EPA) - 480 mg docosahexaenoic acid (DHA) - 220 mg other omega 3 PUFA - 7.6 mg mixed tocopherol</p> <p>FDA recommends maximum of 3 g/day.</p>	<p>online of mercury content of selected fish.</p> <p>PUFA supplements primarily contain purified concentrations of EPA and DHA along with vitamin e (tocopherol) which stabilizes the fatty acids, and supplements may also contain other fat-soluble vitamins such as A or D. These additional vitamins should be accounted for while dosing supplements and monitored if necessary.</p>	<p>significant bleeding and considered safe by the FDA at levels lower than 3 g/day.</p> <p>Hepatic</p> <ul style="list-style-type: none"> - lowers triglyceride levels - LDL and HDL levels can be affected <p>Genitourinary</p> <ul style="list-style-type: none"> - minimally increased risk of prostate cancer and clinical significance is unknown
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L-theanine

Theanine was originally discovered in green tea in the 1950s.[84] Theanine is very similar to glutamate and GABA, both neurotransmitters, its psychoactive effects have been of particular interest.[84-86] It has been noted to have significant anxiolytic properties. One study showed that intake of theanine reduced both subjective reports of anxiety as well as heart rate and salivary response to stressful stimuli.[87] In addition to its effect on mood regulation, glutamate dysfunction has been implicated in the pathogenesis of schizophrenia and therefore theanine is being examined as part of its pharmacotherapy. In multiple studies, adjunct therapy with theanine, in addition to antipsychotics, yielded significant improvement in positive, anxiety, and activation symptoms.[88-90] The mechanism of theanine’s action is still yet to be fully explained, but current studies show that it may stabilize the concentration of glutamate in the brain.[88] However, given that these studies have been brief and with small sample sizes, further long-term studies are needed to substantiate the clinically significant benefits of theanine augmentation.

Could this help Roberto?

When Roberto first started to develop symptoms of anxiety and panic attacks, L-theanine could have been utilized to decrease these symptoms as its anxiolytic properties have been noted in many studies.[87] Although its effect or side effect profile has not been sufficiently studied in children, in adults it is generally a well-tolerated supplement without many known side effects. In addition, when Roberto started to develop positive symptoms of psychosis, l-theanine could have been added as an adjunct to his antipsychotic regimen. L-theanine has been shown to decrease the positive symptoms of schizophrenia as well as concurrent anxiety and activation.[88-90] It is important to monitor Roberto closely for side effects, especially while on sedating antipsychotics as l-theanine can potentiate this effect.

Table 11: L-theanine

Common Dosing	Safety/Monitoring	Adverse Effects
<p>Daily: 200 - 400mg/day either as mono or</p>	<p>In animal models, L-theanine appears to be remarkably safe as</p>	<p>Hypotension</p> <ul style="list-style-type: none"> - Use with caution with

adjunct therapy May be taken as capsules or as liquid tea Maximum Dose: 1200mg/day	very high doses failed to cause toxicity. Toxic doses in humans have also not been reported. Currently, there is no monitoring schedule while taking L-theanine, but blood pressure should be closely monitored as it can cause hypotension.	antihypertensive medications. Chemotherapy - May potentiate the effects of chemotherapy agents. Sedation - Use caution with other sedating agents as L-theanine may have an additive effect.
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Zinc

Zinc is an essential trace element necessary for proper functioning of enzymes, protein, and genes. Zinc plays an important role in brain development and function. Poor dietary zinc intake or malabsorption for an extended period (4 weeks or more) can deplete the brain's supply of zinc and impair function. Chronic zinc deficiencies may impair the growth of a child or adolescent, delay onset of puberty, weaken the immune system, lead to premature birth in a pregnant female, alter one's mood, impair memory, and possibly precipitate psychosis in some individuals. Zinc supplementation in children at risk for deficiency has shown to improve growth and weight gain.

Researchers have found that people with schizophrenia have low blood levels of zinc compared to people without mental illness. One barrier for researchers and clinicians is the difficulty in accurately measuring elemental zinc within the brain because systemic zinc levels do not always reflect the concentration in the brain. Providing zinc supplementation in those at risk for deficiency may reduce some of the symptoms of psychosis, though safety and efficacy has not been established when using zinc supplements as adjunctive treatment for a psychotic disorder.[91]

Table 12: Zinc

Common Dosing	Safety/Monitoring	Adverse Effects
- One study prescribing zinc as adjunctive treatment for children with ADHD used zinc sulfate 55 mg daily PO which contained 15 mg elemental zinc daily. - Absorption of elemental zinc via the GI tract is increased	- Considered safe when taken at tolerable upper intake level per day. - Use with caution in pregnant and lactating women. Zinc given above the tolerable upper intake level is contraindicated in well-nourished pregnant and lactating women. - Prolonged exposure to high levels of zinc per day (above tolerable upper intake level) can lead to chronic adverse effects.	GI - metallic taste (most common), nausea, vomiting, abdominal cramping, diarrhea, anorexia Hematologic - suppresses immunity - decreases copper stores - anemia Hepatic - lowers HDL cholesterol levels

when given with Vitamin B6.	<ul style="list-style-type: none">- Regular monitoring recommended for adverse effects when prescribing high doses and/or over a long period of time. <p>Drug-Drug Interactions:</p> <ul style="list-style-type: none">- Zinc may prevent absorption of some antibiotics- Should be taken at least 2 hours apart from foods containing iron or iron supplements, grains, and legumes.	Genitourinary <ul style="list-style-type: none">- urinary tract infection- nephrolithiasis
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APPENDIX 1: Glossary of Terms

APPENDIX 2: Antipsychotic medication chart

APPENDIX 3: Antidepressant medication chart

APPENDIX 4: Mood-stabilizing medication chart

APPENDIX 5: Anxiolytic and sedative hypnotic medication chart

APPENDIX 6: Attention and concentration medication chart

APPENDIX 7: Scales for evaluating abnormal movements/akathisia

APPENDIX 1: Glossary of Terms

Activation—irritability, agitation, and restlessness which can occur in young people after starting an antidepressant; sometimes also referred to as “the activation syndrome.”

Adjunctive—Adjunctive treatments are those therapies given in addition to a medication and/or treatment to enhance the effect of the primary treatment. For example, someone receiving cognitive behavior therapy (CBT) for anxiety may only partially respond to the therapy and so a practitioner might add sertraline (a serotonin-reuptake inhibitor, SRI) to enhance the effect of CBT.

Affective blunting—This is part of the mental status examination category of affect where a practitioner studies the facial expression of an individual. The person’s facial expression changes little even through parts of the conversation that may be humorous, light-hearted, sad, frightening, surprising, or disturbing. Affective blunting resulting in complete loss of facial expression is considered “flat.”

Agranulocytosis—Granulocytes are immature white blood cells, the pre-fix “a” connotes lack of, and the suffix “osis” refers to a state or condition. This term refers to the body failing to make white blood cells. This is a potential side-effect of the antipsychotic medicine clozapine and thus use of clozapine necessitates registry with Clozapine Risk Evaluation and Mitigation Strategy system (REMS at www.clozapinerems.com). Individuals must have their blood drawn every week for the first six months of treatment, every-other-week for the next six months, and then every month thereafter for the duration of treatment with clozapine. A pharmacist will not dispense this medicine unless they see that the individual has an adequate white blood cell (WBC) count and absolute neutrophil count (ANC).

Akathisia—A movement disorder associated with antipsychotics and some other medications that is characterized by a sense of inner restlessness often leading people to pace, shift their weight from one

foot to the other, or squirm and fidget in their seat. Some people describe this side-effect at its worst as causing them to feel like their “bones are itching or on fire.”

Allopathic—Traditional disease identification and remedy strategy as practiced in Western medicine. People who obtain “MDs” (Doctor of Medicine degrees) attend “allopathic” medical schools. A close cousin, the osteopathic medical tradition emphasized preventive care and the body’s capacity to heal itself. Osteopathic practitioners are “DOs.” These stand in contradistinction to naturopathic practitioners who may use herbs and natural medicine, holistic approaches involving treatments for which there may be some evidence of safety and utility, but are not approved or monitored by the Food and Drug Administration (FDA).

Anticholinergic—A medicine which blocks acetylcholine in the nervous system. Anticholinergic activity in the brain often makes people sleepy, sluggish, and less cognitively engaged. Blocking acetylcholine receptors in the body can result in dilation of one’s pupils, constipation, a dry mouth, and urinary retention.

Antidepressants—Medications which alter neurotransmitter functioning in the brain leading to a decrease in symptoms of depression. Since many of the “antidepressants” also address other mental health needs, such as anxiety disorders, there is a move to rename psychotropic medications by their mechanism of action. For example, instead of calling duloxetine an “antidepressant,” a physician who is prescribing this medicine to help reduce their patient’s pain (not related to depression) might say to their patient: “I would like to prescribe for you a serotonin-norepinephrine reuptake inhibitor (SNRI) which helps reduce the intensity of pain in many people with your condition.”

Antiepileptic—Also called “anti-convulsants,” medications in this class reduce rapid, uncontrolled firing of nerves (neurotransmission) in the brain, therefore suppressing seizures. They can do this via a variety of mechanisms, from stabilizing cell membranes to enhancing the function of inhibitory neurotransmitters like GABA. Anti-epileptics are important to psychiatry because they help treat bipolar disorder (functioning as “mood stabilizers”) and may be useful as adjunctive treatment in schizophrenia-spectrum disorders.

Antihypertensive—Medications which lower blood pressure. The most useful medications in this class are those that not only lower blood pressure (what is known as a surrogate outcome) but those that help prevent cardiovascular problems including stroke and heart attack.

Antipsychotic—These medications block dopamine transmissions in the brain. They do this by blocking the post-synaptic receptor for dopamine (the structure on the dendrite of the receiving neuron that “catches” the neurotransmitter). The area of dopamine transmission that is responsible for hallucinations and delusions appears to be the mesolimbic pathway. Unfortunately, antipsychotics also impact three other areas of dopamine transmission: the basal ganglia, the mesocortical pathway, and the tuberoinfundibular pathway. Blockade of dopamine receptors in these pathways is what causes side-effects.

Anxiety—A subjective sense of worry and array of physical and mental symptoms. The fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual (DSM 5) notes that for any worry to crossover into a formal anxiety disorder (such as Generalized Anxiety Disorder, Specific Phobia, or Separation Anxiety Disorder) one’s relationships, work, school, or other areas of functioning must be impacted.[61]

Attention-deficit/Hyperactivity Disorder (ADHD)—A neurodevelopmental disorder featuring attention problems, difficulties with hyperactive and often impulsive behaviors that is highly heterogeneous with many genetic and environmental factors contributing to whether one develops this disorder. As defined by the DSM5, one must clearly show signs of the disorder by age 12, show signs of it in multiple settings (in other words, not just at home or not just at school), and other causes of inattention or hyperactivity must be ruled out. Regarding this latter point, it is key to check hearing and vision, discover if one is hungry, or if one is anxious due to problems at home before assuming a lack of focus is caused by ADHD. The use of rating scales to collect collateral data may be helpful in diagnosing this disorder.[61]

Attenuated psychosis—“Attenuated” is an adjective which means reduced in force or effect. An attenuated psychotic symptom is a low-level, mild experience such as when someone might complain that they hear their name whispered and glance around to find no one there. These symptoms are often not overly bothersome to the individual. The Attenuated Psychosis Syndrome is a construct that was included in the DSM 5’s “Conditions for Further Study” and describes a condition that impacts young

people (ages 15-25) where someone has intact insight into the symptom with a risk of developing a full psychotic disorder that is “18% in 1 year and 32% in 3 years.”[61]

Benzodiazepines—Medications which enhance the function of the neurotransmitter GABA and may be used to treat a variety of conditions, including panic and anxiety, seizures, alcohol withdrawal, and catatonia.[61]

Bipolar disorder—Characterized by typically alternating periods of mania or “manic episodes” and depression. The DSM5 lists two subtypes, Bipolar I and II, with the two differing in that Bipolar II disorder is characterized by hypomanic rather than manic episodes.

Brief psychotic episode—A condition wherein someone experiences significant psychotic symptoms and meets criteria for schizophrenia, and the symptoms last more than 1 day but less than 1 month in duration.[61]

Capgras Syndrome—also called Capgras delusion, this is a psychiatric symptom wherein the sufferer believe that people close to them have been replaced by impostors. For example, an individual may become overwhelmed by the notion that his parents have been replaced by government officials. Like other delusions discussed in this guide, Capgras phenomena can occur as part of many different mental disorders including bipolar mania and schizophrenia-spectrum illness.

Cognitive Behavioral Therapy (CBT)—The most researched and a commonly used modality of talk therapy in which a therapist focuses on exploring the relationship between one’s thoughts, feelings, and behaviors. The individual participating in therapy is guided through changing unhelpful thinking styles and behaviors to address emotional distress.

Complementary and Alternative Medicine (CAM)—Non-pharmacological interventions, such as mind-body medicine (yoga, mindfulness, acupuncture), that are not traditionally part of Western (allopathic) medicine. This also includes use of products, such as herbs and supplements, which have pharmacological properties but are not regulated by the Food and Drug Administration (FDA).

De Clérambault Syndrome—also referred to as an “erotomanic delusion,” this is a psychiatric symptom that was first characterized by French psychiatrist Gaetan Gatian de Clérambault in the early 20th Century. The central feature of this phenomena is that the individual with the delusion believes that a person with whom they may have had very limited contact and sometimes no social connection at all, is in love with them. Sometimes the person with this type of delusion believes that a famous actor, pop star, politician, or athlete is sending them signals—via social media or over the internet—and that a conspiracy against them making a connection threatens this perceived (imagined) relationship. This may occur as part of many different psychiatric disorders—including bipolar mania, schizophrenia-spectrum disorders, or a more isolated delusional disorder.

Depressive episode—A clinical syndrome with a variety of symptoms that can include: depressed mood, problems sleeping (too much or too little), decreased interest in enjoyable activities, feelings of excessive guilt or worthlessness, low energy, difficulty concentrating, severe changes in appetite (overeating or not eating enough), feeling like one is either weighed down or amped up, and thoughts of suicide. Five or more of symptoms must occur for most of the day, most days of the week for at least two weeks to be considered a depressive episode.[61]

Discontinuation syndrome—After abruptly stopping certain medications (typically serotonergic medications), an individual may experience distressing, but not life threatening, symptoms including dizziness, fatigue, nausea, and headache.

Dopamine—An important neurotransmitter that plays important roles in motor function, sensory awareness, and motivation. Too much production of dopamine in specific areas of the brain is thought to be the cause of psychotic disorders such as schizophrenia. The antipsychotic medications generally work by blocking the action of dopamine.

Dystonia—An involuntary contraction of a muscle. A muscle or, group of muscles, gets very stiff whether a person intends it to or not. Think of your bicep flexing and not having the ability to relax it!

Electrocardiogram (EKG/ECG)—A non-invasive medical procedure that produces a tracing of the electrical activity of the heart. This is performed by placing stickers on areas of the chest. Some

medications can cause changes in heart rhythms, making this test a necessity to screen for potential serious issues.

Evidence-based medicine (EBM)—An approach to guide medical decision making. It emphasizes three pillars: use of high quality research, clinical expertise, and the values of the client.

Executive function—The ability of the brain to carry out complex tasks and achieve goals. These abilities include the ability to maintain attention, effectively utilize working memory, transition between tasks, reason, and engage in complex problem solving.

Extrapyramidal symptoms (EPS)—A group of side effects that can be caused by antipsychotic medications. They result from blocking the action of dopamine in certain areas of the brain. This includes akathisia, parkinsonism, dystonia, and tardive dyskinesia.

Food and Drug Administration (FDA)—The FDA is a government agency that regulates food safety, tobacco, medications, vaccines, blood transfusions, medical devices, and more. Every medication prescribed by a physician is required to be approved by the FDA. This does not include herbs or supplements. To obtain FDA approval, a medication must undergo extensive testing showing that it is both safe and effective.

FDA Black Box Warning—If the FDA determines that a medication has the potential to cause serious harm, it can issue a “black box warning.” This is the most serious warning that the FDA can issue. It requires that a medication have a specific label to warn prescribers about the serious adverse effects or special problems associated with the medication. This information must also be listed in the Physicians Desk Reference and featured on the websites of both the FDA and the manufacturer. Prescribers may still prescribe medications that contain black box warnings, but they must inform patients of the risks involved in taking these medications and the risks of choosing alternative treatments so that patients can make an informed decision.

FDA Indication—This specifies the FDA has found sufficient evidence that a medication treats a specific disease or condition effectively. As a result, the manufacturer can market the medication for that specific

disease/condition. This is often done through information on package inserts and direct to consumer advertisements.

Fregoli Syndrome—also referred to as Fregoli delusion, this term refers to a psychiatric symptom wherein individuals erroneously believe that a loved-one (family member, friend) or acquaintance is disguising themselves in order to spy on them. For example, an individual with a Fregoli delusion may believe her mother disguised herself as a grocery clerk in order to see who she was with at the store and what items they purchased.

GABA—Short for γ -aminobutyric acid. As a neurotransmitter, its main action is to decrease or inhibit activity in the brain by lowering the potential for neurons to excite one another.

Gastrointestinal—A general medical term often used to describe the alimentary track—specifically the stomach, small and large intestines, and anus. Often shortened to “GI.” Medical providers will ask individuals of GI complaints or distress, rather than listing specific symptoms (such as stomach pain, nausea, vomiting, bleeding, cramping, diarrhea, or constipation.) Many psychiatric medications can cause an individual to experience changes in the function of the alimentary track.

Glutamate—An amino acid that acts as neurotransmitter. As a neurotransmitter, its main action in the brain is to excite neurons, making them more likely to pass signals to one another. It is important for learning and memory, however, if there is too much glutamate activity and it is not balanced out by GABA (an inhibiting neurotransmitter), neurons can die.

Gynecomastia—Medical term describing enlarged breast tissue. When this occurs, male breast tissue may begin to resemble female breasts or female breasts may become larger. This condition is not caused by fat accumulation and cannot be solved through exercise and weight loss. This condition is typically caused by an imbalance in hormones. This imbalance is often related to medication use (such as dopamine blocking medications) or can be due to underlying medical issues, such as liver disease or tumors in the testes.

Hallucinations—False or distorted sensory impressions that seem to be real perceptions. These vivid impressions are generated by the mind and not by an external stimulus. While some people think of

hallucinations as only seen or heard, hallucinations can also be felt, smelled, or even tasted depending on the type of sensory impression the mind is creating.

Hemoglobin A1c (HgbA1c)—A blood test that measures the average level of glucose (or sugar) in a person's blood stream over the preceding three months. Normal values for the test are typically in the range of 4%-6%. Results greater than 7% indicate diabetes, which sometimes may be managed through lifestyle modifications or medication changes.

Hyperprolactinemia—Medical term for an excess of the hormone prolactin. Hyperprolactinemia can be caused by medications (particularly those which block dopamine), tumors that push on the pituitary gland in the brain (which releases prolactin), or by tumors that secrete prolactin. Signs and symptoms include milk discharge from the breast, loss of libido, infertility, and breast development in men.

Hypomania/hypomanic episode—Characterized by similar symptoms to a manic episode, such as decreased need for sleep, elevated mood, inflated self-esteem, and increased goal-directed activity, but symptoms are less severe and of shorter duration. Does not require hospitalization and psychotic symptoms cannot be present.

Ideas of reference—A type of delusion in which a person interprets seemingly benign or irrelevant environmental stimuli as being personally significant.

Libido (decreased)—Libido is another word for sexual drive; decreased libido is to experience lower desire for sexual activities as compared to normal for an individual.

Lipids—An organic compound that is found in cell membranes and utilized in energy storage and cell signaling. Colloquially known as "fats." Can be dissolved in alcohol but not in water. A fasting lipid panel helps practitioners learn about the balance between "good cholesterol" (HDL) and "bad cholesterol" (LDL) that contribute to cardiovascular status.

Lithium toxicity—Occurs when serum lithium levels rise above the therapeutic range. Symptoms include, but not limited to, dizziness, nausea/vomiting, abdominal pain, ataxia, and confusion. Symptom severity

may not correlate with serum levels. Lithium toxicity is a medical emergency and requires prompt medical attention. Can lead to coma and death. Individuals may need dialysis to treat lithium toxicity.

Long-acting injectable—Antipsychotic medications that are given intramuscularly and formulated such that the dose is slowly released over time. Typically given by a practitioner every 2-4 weeks.

Mania/manic episode—An episode characterized by decreased need for sleep, grandiosity, elevated mood, racing thoughts, increased goal directed behavior that must significantly impair daily functioning and often requires hospitalization. Manic episodes may feature psychotic symptoms that are hard to distinguish from symptoms of schizophrenia. Mania is more severe and of longer duration than hypomania.[61]

Monoamine oxidase inhibitor (MAOI)—Compounds that inhibit the action of monoamine oxidase enzymes. This prevents the breakdown of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine. These were the first drugs developed to treat depression and anxiety, and can be used in neurologic such as Parkinson's disease. MAOIs are rarely prescribed due to requiring a specialized diet and multiple serious medication interactions. Failure to adhere to the diet restrictions or avoiding certain medications can be life-threatening.

Mesolimbic pathway—Often called the “reward pathway” in the brain. Blocking dopamine transmission in this region of the brain has proven useful in reducing the intensity and frequency of “positive” psychotic symptoms. However, it can also cause affective blunting.

Metabolic side effects—Potential side effects from antipsychotic therapy (primarily second generation antipsychotics or SGAs). Includes weight gain, development of type II diabetes mellitus, hypertension, and abnormal lipid profiles.

Mixed episode—State in which one is experiencing both manic and depressive symptoms concurrently. Must meet full criteria for one of those two states and at least three symptoms of the other state to be called “mixed.”[61]

Myocarditis—Inflammation of the heart. It is a rare, but life-threatening, side effect of clozapine.

Negative symptoms—Disruptions to executive functioning (planning, sequencing, carrying out tasks), overall mental fluidity, and a blunting of affective state that occurs in psychosis.

Neuroleptic malignant syndrome—Potentially fatal reaction to antipsychotic medications that is characterized by altered mental status, autonomic (blood pressure, heart rate, temperature) dysfunction, and muscle rigidity.

Neuroleptic—“Neuro” or nerves and “leptic” or “to stop” or “to halt.” Translates to suppression or halting of nerve functioning. Despite the literal definition, the term is often used interchangeably with “antipsychotic” when describing medications that block dopamine transmission.

Neurotransmitter—A chemical substance that is released from nerve endings (axons) and causes changes to another neuron whose dendrites have receptors for the neurotransmitter. These chemicals are responsible for the “messaging” between neurons. The seven major neurotransmitters are: acetylcholine, dopamine, gamma-aminobutyric acid [GABA], glutamate, histamine, and serotonin.

Norepinephrine—A neurotransmitter. Important for regulating sleep, appetite, mood, and cognition. Disruptions to norepinephrine has been related to apathy, depression, and anxiety.

“Off label”—Refers to the use of a medication for a condition other than that for which it has received Federal Drug Administration (FDA) approval. Many psychotropic medications are utilized in this manner.

Orthostatic hypotension—Low blood pressure caused by changing body positions (such as lying flat to standing up) characterized by dizziness, lightheadedness, and rapid heartbeat.

Paranoia—State of being excessively suspicious towards others, often manifesting in delusional thoughts.

Parkinsonism—Symptoms include tremor, slow movements, stiff muscles, and unstable posture. These symptoms can be caused by Parkinson’s disease or may be a side-effect from antipsychotic medications. More commonly seen with use of the older, first generation antipsychotics.

Placebo group—Control group in a research study who gets the “non-active” treatment.

Positive symptoms—Thoughts and behaviors considered to be outside the range of reality, including hallucinations, delusions, and disordered thoughts and/or speech that occur during psychosis.

Prodromal—Occurring prior to the onset of psychosis, characterized by having subtle signs of changes in mental status, such as social withdrawal, indecisiveness, difficulty concentrating, and anxiety. This state is typically identified retrospectively, but there is research to show that intervention at this stage can be very helpful in terms of overall prognosis.

Prolactin—Hormone secreted by the pituitary gland. It has several functions, including a role in milk production. Levels are affected by dopamine, which suppresses its secretion. Medications that reduce dopamine levels can result in elevated levels of prolactin (hyperprolactinemia).

Prophylactic—An agent or treatment that prevents or protects against development of a disease.

Psychosis—A mental disorder where one experiences loss of ability to determine reality. Is manifested by both “positive” and “negative” symptoms.

Randomized control trial (RCT)—A research design considered to be the gold standard in clinical trials. Participants are randomly assigned to either the active treatment group or no treatment group (control), while other variables are kept relatively constant. This design is often used when studying the effectiveness and/or side effects of a medical treatment or medication.

Salivation—Production of saliva. Sialorrhea (too much saliva) can be a side effect of antipsychotics, particularly clozapine.

Schizophrenia—A disorder that occurs in about 1% of the world’s population. Characterized by both positive and negative psychotic symptoms occurring for a minimum of six months and result in functional impairments. Common treatments include antipsychotic medications and social rehabilitation.[61]

Schizophreniform disorder—A disorder where psychotic symptoms are present for one to six months and cause functional impairment.[61]

Sedation—Inducing sleepiness; can reduce irritability or agitation.

Sedative hypnotic—Medications that induce and maintain sleep states. Problems with some sedative hypnotics include parasomnias (sleep behaviors), disinhibition, and the potential for dependence and abuse.

Seizure—Abnormal, uncoordinated electrical activity in the brain that can cause confusion, loss of consciousness, and/or involuntary muscle movements.

Serotonin—One of seven major neurotransmitters in the brain. Found in the brain, spine, stomach and intestines. Abnormal levels of serotonin have been theorized to cause depressive and anxiety states.

Serotonin syndrome—A medical emergency caused by excess serotonin levels in the body. Symptoms include confusion, anxiety, agitation, sweating, elevated heart rate, increased blood pressure, increased body temperature, tremor, and muscle stiffness. Can be caused by overdoses of antidepressant medication, interactions between multiple medications, and/or use of certain recreational drugs, such as cocaine or 3,4-Methylenedioxymethamphetamine (MDMA or “ecstasy.”)

Serotonin norepinephrine reuptake inhibitor (SNRI)—A medication that theoretically blocks the reuptake of serotonin and norepinephrine by nerve cells, resulting in higher available levels of serotonin and norepinephrine between neurons.

Serotonin reuptake inhibitor (SRI)—A medication that theoretically blocks the reuptake of serotonin by nerve cells, resulting in higher levels of available serotonin between neurons.

Stimulant—Also called “psychostimulants,” these medications increase dopamine activity in the frontal lobes. This leads to increased attention and wakefulness.

Supportive psychotherapy—Involves building a positive relationship, empathic listening, stepwise problem-solving, and helping individuals mobilize internal resources (bolstering “ego” strengths/using healthy coping strategies) and external resources (friendships, family relationships, teachers, mentors, peer support) to manage difficulties.

Tardive dyskinesia (TD)—An involuntary movement disorder associated with use of first generation antipsychotic medications. The tongue and muscles of the face are typically the first effected (e.g. facial grimacing, tongue protrusion.) Can also cause dancelike (choreiform) or jerking movements in the limbs. Can be highly distressing and difficult to treat.

Tricyclic antidepressant (TCA)—Class of antidepressant medications that affect several different receptor sites in the brain. Are used less frequently due to side effect profile and potential lethality if taken in overdose.

Therapeutic dose—Minimum amount of a medication needed to achieve a clinical desired response.

Tinnitus—Experience of sound when there is no external source present, often referred to “ringing in the ears.” Most commonly caused by noise-induced hearing loss but also associated with some medications and health conditions.

Urinary retention—Inability to completely empty the bladder; commonly caused by anticholinergic side effects of medications.

Withdrawal dyskinesia—An involuntary movement disorder commonly associated with the abrupt discontinuation of antipsychotic medications. Not life-threatening and usually resolves within a few weeks. May include tongue protrusion, facial grimacing, dancelike (choreiform) movements of the limbs, involuntary vocalizations, and jerking movements of the neck.