Intro

MC: Hello and welcome to The Med Thread. Today we've got something a little different for you.

CB: As promised, this sequence of The Med Thread episodes will feature students from Memorial School of Pharmacy. They have picked topics that intrigue or questions that they've come across in practice.

MC: The activity we asked the students to do is called evidence-based practice. Now evidence-based practice is essentially using the best available evidence to make a clinical decision. There are always things and updates to medications and many of this we can't teach so our students have to learn how to find new information and to be able to understand it and evaluate it for their patients. In this activity, the students asked a clinical question based on their experiences or just something they're interested in, then they looked at multiple resources including the primary literature and they evaluated that. They came up with an answer and recorded a short segment for the podcast.

CB: This first segment is on bipolar depression. The students ask what makes the treatment of bipolar depression different? A manic or hypomanic shift is something we need to worry about in these patients.

Bipolar depression

Co: Hello and welcome back! This is Courtney,

Y: Yong,

Ca: and Catherine.

Y: We are all third-year pharmacy students at Memorial University's School of Pharmacy,

Co: and this week we welcome you to The Med Thread, a medication information station from the School of Pharmacy at Memorial! Each month this podcast brings you an exciting topic related to medications, disease conditions, pharmacy practice and more!

Y: This week we will be discussing the treatment of depressive episodes in patients with bipolar I disorder who are already stabilized on lithium. What medications can we add on? Which is the most effective? We'll dive into the evidence this week.

Ca: Bipolar disorder is a psychiatric illness characterized by periods of high or elevated and low or depressive moods. Patients with this diagnosis spend periods of time in each of these states, called manic and depressive episodes, and also have periods of wellness when no symptoms are present.

Co: During periods of mania, patients are euphoric or angry or irritable for at least one week with accompanying symptoms such as pressured speech, decreased need for sleep or feelings of grandeur. There is also a less severe form of mania which we refer to as hypomania, which has similar symptoms but usually does not impair a patient's daily functioning.

Y: Depressive episodes are characterized by symptoms such as low energy and mood, feelings of guilt, suicidality or loss of interest in activities that were previously enjoyed by the patient. A person is diagnosed as being depressed when they have at least five characteristic symptoms, most days, for a period of at least two weeks.

Ca: Some patients with bipolar disorder also experience mixed episodes in which symptoms of both mania and depression are experienced at the same time. Briefly, there are subtypes of bipolar disorder. The main subtypes are bipolar I disorder and bipolar II disorder. If a patient has had a manic episode, they are diagnosed with bipolar I disorder. If a patient has only experienced hypomanic and depressed episodes, but never a full-blown manic episode, they are diagnosed with bipolar II disorder. We will be discussing bipolar I disorder today.

Co: So why is this a big deal? Can't we just give someone with bipolar disorder an antidepressant, such as sertraline—an SSRI, when they are depressed?

Y: Not quite! There is a concern about antidepressant monotherapy in patients with bipolar disorder because these medications are known to be associated with a manic or hypomanic switch. This means that depressed patients with bipolar disorder can be flipped into a manic or hypomanic episode as a result of the medication.

Co: So, then what do we do to treat their depression but also make sure they don't have a manic episode?

YK: Well, commonly patients with bipolar I disorder are started on a mood stabilizing medication, such as lithium, when they have their first manic episode. Lithium is also indicated for bipolar depression. But if a patient is already stabilized on lithium and they have a breakthrough depressive episode, I guess we could add something to the lithium?

Ca: Like an SSRI?

YK: Maybe... let's look at what the evidence says.

Ca: We searched the literature to find an answer to our question. What medication is the most effective as an adjunct to lithium for a bipolar I patient currently experiencing a depressive episode? Initially we looked for the answer in the CANMAT and ISBD 2018 Clinical Practice Guidelines and the Compendium of Therapeutic Choices produced by the Canadian Pharmacists Association.
(Yatham, 2018)

Co: These sources laid out several treatment options: adjunctive quetiapine, lurasidone, or lamotrigine. From here we decided to search for systematic reviews and meta-analyses comparing these adjunctive therapies in the treatment of bipolar I depression to each other, but to no avail!

Y: So instead we searched for randomized controlled trials comparing each of these medications as adjunctive treatments with lithium as compared to placebo and to evaluate the validity of these trials. We found RCTs comparing adjunctive lamotrigine and lurasidone to placebo in the treatment of bipolar I depression for patients stabilized on lithium, but no studies for quetiapine in this setting.

Ca: Before we dive into more details about the trials, we'd like to quickly define some acronyms that will come up in the conversation. DSM-IV criteria is a set of characteristics outlined in a guide published by the American Psychiatric Association that can be used to diagnose Bipolar Disorder. MADRS score is a depression rating scale. A higher score indicates more severe depressive symptoms. CG-BPI score is similar to MADRS score, another depression rating scale. MINI-Plus interview is a structured diagnostic interview instrument for psychiatric conditions.

Co: We critically appraised the randomized placebo-controlled trials we found regarding lamotrigine and lurasidone. The lurasidone trial enrolled patients 18-75 years of age diagnosed with bipolar I disorder who were stabilized on background lithium or valproate. The patients met the DSM-IV criteria for a major depressive episode. They evaluated change in MADRS scores from baseline to week 6.
(Loebel, 2014)

Y: That study was well performed, but although it was a randomized, double-blind placebo-controlled trial, the authors did not perform a true intention-to-treat analysis, resulting in 8 patients who were initially randomized not being accounted for in the analyses. However, this should not impact the validity of the results too much.

Ca: And the important primary and secondary outcome measures, including a greater than 50% reduction in MADRS total at 6 weeks, were statistically significant in favour of lurasidone.

Co: The lamotrigine study enrolled outpatients 18 years of age or older with bipolar I or II disorder on background lithium with a current major depressive episode confirmed by MINI-Plus interview.
(van der Loos, 2009)

Ca: That study was also well-performed with no major red flags in trial methodology and it detected a statistically significant decrease in MADRS score from baseline to week 8 in favour of lamotrigine. But there was no statistically significant decrease in patient response, which was defined as a greater than 50% reduction from baseline in MADRS and/or CG-BPI, another depression rating scale, between the two groups.

Y: Both of these trials were of adequate length to assess efficacy of treatment for depression. It is important to note that both of these trials excluded patients who were an imminent suicide risk or who had a history of alcohol or substance abuse.

Co: So where does that leave us? What do we recommend?

Ca: Psychiatric medicine seems to be a bit of an art. Realistically, adjunctive quetiapine, lurasidone or lamotrigine would all be appropriate. The initial treatment choice would depend on patient-specific factors like insurance and what adverse effects they are most willing to tolerate. Our recommendation may have changed if we were able to find a study comparing the agents to each other, but that is the tricky side of evidence-based medicine, we can't always find what we want! Quetiapine is cheaper and also more likely to be covered.

Co: Based on the evidence, lurasidone seems to be more effective than adjunctive lamotrigine, and we didn't find a comparable RCT with quetiapine. But given that quetiapine and lurasidone are

in the same class, second generation antipsychotics, we might be able to assume a class effect and try quetiapine first. Lurasidone is special authorization under NLPDP (Newfoundland and Labrador Prescription Drug Program), but quetiapine is an open-benefit.

Y: The bottom line is that the best treatment should be tailored to your individual patient. N-of-1 trials do have the least risk of bias! Thanks for joining us on our journey into the evidence on this episode of The Med Thread.

Treatment resistant depression

CB: Next is a segment on treatment resistant depression. What do we do if the typical first-line treatments don't work? What does the evidence say about aripiprazole, a medication that seems to be used a lot?

H: Hi everyone! This is Hannah,

A: I'm Avery,

M: and I'm Mario.

H: We are third-year pharmacy students at MUN and this is our first podcast with The Med Thread.

A: Today we will be providing a summary of the evidence we have found on specific topic of in the area of treatment resistant unipolar depression.

H: Mario came up with a question while working in a pharmacy and we focused our search for evidence there. Mario, can you explain why this question came up?

M: Sure! Our generation has brought forward an era where the silence that used to surround mental illness no longer exists. I have many close family and friends who are experiencing or who are currently treated for a mental illness. As a pharmacy student, it is not a surprise these individuals may come to you looking for support or with questions surrounding their illness and medications. I began to gather an interest in therapies surrounding mental illness, such as treatments for depression. At the pharmacy, I noticed that many patients were on different therapies and there were many different types of combinations associated with treatment-resistant depression. I was interested to know what was the next step after an initial treatment failure? Was switching medications the best option? Was adding a medication the best option? If so, which one was more effective than the others? At the time of choosing my research question, I shared a very personal experience with a patient at my pharmacy who unfortunately went through an episode of serotonin syndrome while initiating a triple therapy for depression and this was very eye opening. And this is what challenged me to consider further the treatment of depression and used these experiences towards this podcast today.

H: I also had an interest in the increasing use of aripiprazole (or Abilify) in treatment resistant depression. Abilify is an antipsychotic not routinely used for depression. But I have been seeing more family doctors prescribing this antipsychotic and I was interested to see what the evidence is out there for its use.

A: We came up with a specific clinical question to help narrow our search a little better and our clinical question was based on the following fictitious scenario.

ML: Anna Baker is a 23-year-old female suffering from treatment resistant depression. Initially Dr. Smith started Anna on venlafaxine and then continued to switch her to citalopram since she had no response to venlafaxine. Dr. Smith is now wondering if a combination therapy would be best for Anna. He would like to keep her on citalopram since she had a partial response to this medication, and he would like to add an adjunctive therapy. He would like to know if there is good evidence supporting the use of aripiprazole, as he heard that this newer drug has a lot of evidence for benefit in depression.

A: To answer this question, we had come up with a search strategy. To do this we formulated a PICO question which was as follows: "In adult women with treatment resistant unipolar depression, is citalopram more effective in combination with aripiprazole in reducing symptoms of depression compared to citalopram monotherapy?" In this setting, unipolar is used to differentiate her type of depression from bipolar disorder. Treatment resistant depression means that at least 2 previous trials of different antidepressants was tried.

H: We used 5 sources to try to answer this question. Pubmed and Embase for primary literature, UpToDate for a general recommendation and, clinical practice guidelines to get a picture of what is are the best practice recommendations used today.

A: My searches included spending some time looking at PubMed, which is a primary resource for study trials and the World Federation of Societies of Biological Psychiatry and that's kind of like an international clinical practice guideline. During my searches I came across some pretty useful data. Firstly, aripiprazole was found to be significantly more beneficial compared to antidepressants alone but caused more unwanted effects. This additional side effect profile would have to be conveyed to the patient and a risk vs. benefits analysis completed. Secondly, in patients that were unresponsive to a single SSRI agent, such as citalopram, aripiprazole was associated with a high rate of conversion from non-responders to responders. It is also important to note that aripiprazole, as indicated by its monograph, is use as an adjunct to antidepressants for the treatment of Major Depressive Disorder in adult patients who had an inadequate response to prior antidepressant treatments during the current episode.

M: I spent most of my research time on CPG Infobase, which is the clinical practice guidelines. this database was entirely new to me, but I found it to my liking. The Canadian Clinical Practice Guidelines contains approximately 1,200 evidence-based guidelines developed or endorsed by authoritative medical or health organizations in Canada. All of the information I'll be speaking of was found in one article named the "Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder," specifically Section 3 under Pharmacological Treatments. The article begins to assess how to manage inadequate responses to an antidepressant.
(Kennedy, 2016)

The STAR*D Trial, which stands for "Sequenced Treatment Alternatives to Relieve Depression", was a collaborative study which focused on the treatment of depression when initial therapy proved inadequate. They stated that "patients who tolerated citalopram and who had partial

response were more likely to benefit from adjunctive strategies compared to switching."
(Gaynes, 2012)

A network meta-analysis comparatively analyzed the efficacy, acceptability, and tolerability of various augmentation adjunctive agents in adult patients with treatment-resistant depression. They authors stated that "as adjunctive agents, there are stronger efficacy estimates for both aripiprazole and quetiapine when compared to other adjuncts."
(Zhou, 2015)

A small prospective cohort study included in the CPG guidelines stated that "adjunctive aripiprazole was superior to antidepressant switch on efficacy outcomes, including response and remission.
(Han, 2015)

And finally, Aripiprazole is considered first line as "recommendations for adjunctive medication for nonresponse or partial response to an antidepressant" according to CANMAT guidelines. This last statement strongly supports our initial question, that there is good evidence supporting the use of aripiprazole as an adjunct.

HG: I spent a lot of time using Embase to answer our clinical question and there were 3 studies I would like to briefly mention which may answer the question. First was a randomized control trial that compared aripiprazole when used as combination therapy with SSRI or SNRI or a switch to bupropion alone. They found that aripiprazole combination therapy was successful in increasing responsiveness to treatment and was modestly better than bupropion. However, they noted significant side effects such as weight gain, extrapyramidal side effects and restlessness. Unfortunately, with this study, and with a lot of studies we see, the trial was conducted for only 12 weeks and there were only about 250 participants. As a result, the results are significant but are not so much different that we can say that it is meaningful information to use in practice or clinically relevant. As well, the 12-week limitation means that we are not able to predict how an aripiprazole combination therapy would affect our patients after 3 months.
(Mohamed, 2017)

Another trial with about 400 patients was a double blind RCT that directly compared the use of sertraline with aripiprazole and sertraline monotherapy. They found that aripiprazole in combination with sertraline significantly improved clinical depression outcomes and was well tolerated in their patients. They concluded that aripiprazole was a viable option for people who are not responding to sertraline alone. It should be noted that this study was conducted for only 6 weeks. Even though this study used sertraline, we feel that it is appropriate to use this information with our case on citalopram because both sertraline and citalopram have the same mechanism of action where they are both selective serotonin reuptake inhibitors.
(Kamijima, 2018)

Finally, a systematic review of atypical antipsychotics in the treatment of refractory depression looked at 6 open label trials and 3 RCTs studying aripiprazole as adjunctive therapy with various antidepressants. They found that the evidence supports the use of aripiprazole in treatment resistant major depressive disorder. Although they said that the extrapyramidal side effects known to aripiprazole such as restlessness, was a common reason to discontinue therapy.
(Wright, 2013)

A: So overall, the conclusion that we were able to come up with is as follows:

M: In adult women aged 20-30 years old, who have failed two single agents for unipolar depression, aripiprazole in combination with citalopram is more effective when compared to citalopram monotherapy.

H: Aripiprazole adjunctive therapy has been proven to be superior than switching the original antidepressant. Aripiprazole is considered a first line agent for adjunctive therapy in the event of no response or partial response to an antidepressant.

A: It was also proven to be safe and effective with only a slight increase in adverse side effects.

H: After we discovered this evidence, we were able to come up with a few questions that may address any knowledge gaps in our scenario. Question one is how long does it take to see an effect with aripiprazole? The answer to this question is: The onset of action of Aripiprazole is roughly 1-3 weeks but it may take up to a full 8 weeks in order to experience the full effects of this medication.

A: Question two is how long should treatment with aripiprazole last for? The clinical trials using aripiprazole ran for about 8 weeks on average, so it is difficult to answer this question based on the evidence alone. The answer to this question based on our clinical judgement is this: A specific length of treatment for depression is rarely given, instead, depression among each individual is unique with respect to contributing factors and patients should only be discontinued when they feel they are ready to do so on their own terms.

ML: In conclusion, I believe there is continued research that must be done on the topic of treatment resistant depression. Our research proved that citalopram and aripiprazole combination offer improved outcomes but in practice there are so many combinations of antidepressants used. As I had previously mentioned, mental health is no longer a hidden topic of conversation and I believe physicians and pharmacists alike must be kept updated on current guidelines and evidence to provide the best possible treatment outcomes for our patients.

Depression in children

CB: And lastly, let's look at depression in children. What options do we have? What are the risks of using medications in these brains that are still growing?

A: Hello and welcome! This is Allison, Luke, Emily, and Nicole and we are super excited to be featured on this episode of The Med Thread. We are third year pharmacy students at MUN School of Pharmacy. Everyone is affected by mental illness one way or another and 1 in 5 people will personally experience a mental health illness. Today we will be talking about the best treatment for depression, specifically in children.
(Canadian Mental Health Association. https://cmha.ca/about-cmha/fast-facts-about-mental-illness)

E: While researching the best treatment for depression in children, we turned to resources such as Clinical Practice Guidelines, and research databases like Pubmed. We focused on meta-analysis or randomized control trials as they are the best research trials to answer therapeutic questions.

N: The treatment of depression in children and adolescents is often misunderstood and underdiagnosed due to the lack of evidence and randomized controlled trials completed in children and adolescents. A reason for this is that it might not be possible or ethical to conduct randomized controlled trials because it may inflict self-harm upon children who participate in the study while taking an antidepressant. There is also evidence showing an increased risk of suicide associated with treatment of depression in children and adolescents.
(Garland, 2016)

Therefore, the best treatment of depression in children and adolescents is one that improves overall mood and reduces depression while also having a good risk versus benefit profile. The first line options are Cognitive Behavioral Therapy (CBT) and Intrapersonal Therapy (IPT). CBT is psychotherapy that treats problems and boosts happiness by modifying dysfunctional emotions, behaviors, and thoughts. IPT is a form of psychotherapy that focuses on relieving symptoms by improving interpersonal functioning. It addresses current problems and relationships rather than childhood or developmental issues. Second line choices are pharmacological options which include fluoxetine, sertraline, citalopram, and escitalopram. These drugs are in a class known as selective serotonin reuptake inhibitors, or SSRIs in short. In individuals younger than 18, Health Canada has not approved any antidepressant medication. The FDA has approved fluoxetine in those 8 years and older and fluoxetine and escitalopram are improved in individuals 12 years and older.
(MacQueen, 2016)

L: So how does an SSRI work? Serotonin is a neurotransmitter found in the brain that is known as the happy chemical because it contributes to wellbeing and happiness. The ways that SSRIs work to increase the amount of serotonin in the brain is by stopping the reabsorption of the chemical at the presynaptic neuron. This leads to more serotonin available in the synapse to be taken up by the postsynaptic neuron. And once the chemical is absorbed postsynaptically, it leads to an increase in nerve transmission which has a direct effect on happiness and wellbeing overall.

E: To give you guys a brief history of the SSRIs, in the 1960's, evidence began to show that serotonin was a key chemical involved in depression, and there was found to be lowered amounts in people of depressive suicides. This association lead to pharmaceutical companies exploring the potential role of drugs that act on serotonin in treating depression. SSRIs selectively block serotonin reuptake to increase the amount of serotonin available in the brain to stimulate serotonin receptors. Stimulation of serotonin receptors in the brain is a key process involved in creating feelings of pleasure and happiness. These drugs, by allowing more serotonin to stimulate their receptors in the brain, thereby increase feelings of happiness and help treat depressive symptoms. In the 1970s, fluoxetine was first suggested as a possible SSRI antidepressant. Later, it was found that fluoxetine was a potent SSRI with little affinity for the norepinephrine transporter, which paved its way of becoming the first drug in the SSRI antidepressant category. In 1987, FDA first approved fluoxetine in the US and 2 years later, it was approved by Health Canada as well. Since the development of fluoxetine, there have been several other SSRIs approved in Canada such as sertraline, citalopram, paroxetine, escitalopram, and fluvoxamine. The SSRIs have played a massive role in the treatment of depression since their development, specifically in children. We will be focusing on the SSRIs today, however Luke will give a brief summary of other antidepressant classes and discuss why they are not the drugs of choice for treatment of depressive symptoms in children.
(Hillhouse, 2015)

L: Some other classes of antidepressants that are used for treatment of depression in adults include monoamine oxidase inhibitors, tricyclic antidepressants, bupropion, and Serotonin-norepinephrine reuptake inhibitors. There is insufficient data regarding these drugs and their use in children for them to be considered pharmacological option. This is likely due to the safety profile currently in adults including multiple adverse reaction events. Monoamine oxidase inhibitors are currently third-line in treatment of depression for adults due to interactions with other drugs and food, such as cheese, that can lead to possible hypertensive crisis which is likely why it is not indicated in children. Tricyclic antidepressants are not recommended because of potential cardiotoxicity in overdoses. SNRIs are similar to this because of increased effect at norepinephrine receptors there is a greater chance of side effects including nervousness, dizziness and potential hypertension. This is why the use of SSRIs is considered first in pharmacological treatment of children.
(Kennedy, 2018)

N: After reviewing studies focusing on treatment of depression in children, SSRIs have proven to be the safest and most effective option of treatment. Given all available data to date it appears far more likely that SSRI use decreases suicide rates rather than increases them. The potential benefits of SSRI use outweigh the potential harms for the treatment of depression in children and adolescents, and as maintenance treatment, SSRI antidepressants reduce the risk of relapse and recurrence of depression. Therefore, SSRIs are the primary class of antidepressants used in children, which is why the focus has been centered on this class.
(Korczak, 2013; Garland, 2016; Vitiello, 2016)

E: After focusing on the class of SSRIs we really zoomed in on which specific SSRIs would be best in the treatment of children and that's where we came up with the answer that fluoxetine is the drug of choice to treat depression in children. After evaluating multiple studies, a consensus has been reached that fluoxetine is the drug of choice to treat depression in children. Fluoxetine has shown superior improvement in depressive symptoms and clinical assessment after 5 weeks compared to placebo. Fluoxetine has been chosen over other SSRIs in the class because the risk benefit for fluoxetine and children and youth depression is favourable, while it is less clear for other SSRIs. It is also noted that fluoxetine is associated with the fewest reports of discontinuation symptoms. Not to mention, fluoxetine is also available in liquid formulation, which is preferable for children who are unable to swallow capsules.

There has been concern that using drug therapy to treat depression in children can increase the risk of suicide-related events, such as suicidal thoughts. Studies have revealed that the risk of suicide associated with untreated depression is likely greater than that associated with appropriate SSRI use. To put it in perspective, every 2 out of 100 people treated with an SSRI will have a "suicide-related" event compared to 1 out of every 100 people treated with placebo as shown by a study. This shows that the risk of increased suicide events while taking SSRIs is not significant by any stretch. Fluoxetine, out of the SSRI class, has the most evidence that supports its use for treatment of depression in children. The TADs trial, which Allison will discuss next, explores the efficacy of fluoxetine and cognitive behavioural therapy in particular.
(Emslie, 1997; Garland, 2016)

A: TADS stands for Treatment for Adolescents with Depression Study. The trial was a randomized controlled trial designed to compare efficacy of fluoxetine alone, cognitive behavioural therapy alone, a combination of the two, and placebo. This study was based on research at the time

concluding that cognitive behavioural therapy for treatment of major depressive disorder was supported and from the randomized controlled trial done by Emslie et al. that looked at the age group 7-17, that showed that fluoxetine was better than placebo. The TADS trial looked at the age group 12-17. Fluoxetine began at a starting dose of 10 mg/day, which was then increased to 20 mg/day at week 1 and, if necessary, to a maximum of 40 mg/day by week 8. The study by Emslie et al. looked at fluoxetine at 20 mg/day. The conclusion of the TADS trial was that fluoxetine and cognitive behavioural therapy together were most effective and had the greatest improvement in suicidality. It was superior compared to placebo, fluoxetine alone, and cognitive behavioural therapy alone. As well, cognitive behavioural therapy can protect against harm related adverse events that could be experienced while taking fluoxetine.
(March, 2004)

N: In summary, the first line of treatment for depression in children and adolescents is cognitive behavioural therapy or intrapersonal therapy. The second line of treatment are SSRIs, where fluoxetine is the drug of choice. As seen in the TADS trial, the most effective treatment option for depression in children and adolescents is combination therapy of cognitive behavioural therapy or intrapersonal therapy with fluoxetine. This can be used in practice to maximize the treatment of depression in this population. That being said, the treatment of all individuals for depression should be done on an individual basis, identifying any special considerations, and needs for the patient. I hope you all enjoyed this episode of The Med Thread. I'm Nicole, this is Emily, I'm Allison, and I'm Luke. As always, thanks for listening!

MC: In the short time they had here, many more questions can be raised. And if you're interested about it or would like us to talk more about these topics, send us an email at medthread@mun.ca. And tune in next month, when we have more students talking about their questions and answers. Thanks for listening!

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