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UW Honors Program -Senior Honors Project Write Up

A Clinician's Guide to the Pharmacologic Treatment of Pediatric Major Depressive Disorder

JM is a 14-year-old female admitted to the pediatric unit on a 72 hour holding policy after her father found her unresponsive and brought her to hospital. After regaining consciousness, patient reports taking “the rest of the bottle” of Benadryl at home in an attempt to “not be here anymore.” JM is medically stable by the following morning and is able to participate in a patient interview. She reports that her act was a result of feelings of abandon by her mother, financial difficulties facing her family, continual teasing from classmates and “just feeling sad.” There is no documented family depression but father reports the child mother “is bipolar.” She is not taking any medications currently and has been in counseling at her school for the last 6 months. The question now facing her care team becomes is she a candidate for medical management for her pediatric depression and what is the approach to her patient specific treatment plan.

Pediatric depression is an increasing problem facing healthcare providers today and knowing how to appropriately screen and treat a patient for pediatric depression is something new clinicians need to feel comfortable with. The following is a guide to be used by any healthcare professional, but particularly pharmacy students, in assisting in the treatment and management of this condition.

- Epidemiology and Prevalence
 - <13 yo
 - 2.8%
 - 13-18 yo
 - 5.6%
 - ~60% will have recurrences in adulthood
- Concern for increased prevalence later in life if not properly managed in childhood

- One study examined children without depression who were 9-13 yo > than 7% of boys and almost 12% of girls developed a depressive disorder by the age of 16
- Risk Factors
 - Parental depression- 3 fold
 - Health condition (diabetes, asthma)
 - Family history
 - Female
 - Puberty/Hormonal changes
 - Low birth weight
 - Maternal age <18
 - Obesity
 - Anxiety/learning disorders/sleep disorders
 - Psychological risk factors
 - Low self esteem, negative body image
- Screening
 - Screening not recommended in children
 - Unable to use the tools we have available due to lower than needed level of cognition and communication
 - Recommend screening in primary care for adolescents 13-18 yo
 - Several options for screening tools
 - Beck Depression Inventory for Primary Care (BDI)
 - 12-18 yo
 - Self report
 - Children's Depression Inventory (CDI)
 - 7-17 yo
 - Self report, parent report, or teacher report
 - Children's Depression Rating Scale- Revised (CDRS-R)
 - 6-12 yo
 - Child, parent, and/or teacher
 - Diagnose and monitor treatment response
 - Most commonly used in clinical studies
 - Gold standard in evaluation of response to treatment in clinical trials
 - Multiple other options
- Diagnosis
 - Diagnostic criteria are the same for adults with the potential for a different presentation outlined in both the DSM IV and DSM V
 - Part of diagnosis is rule out of other potential causes, differential is crucial
 - Must assess suicide risk
 - Important consideration for treatment
 - Patient safety is our number one concern
- Diagnostic Criteria- 5 of the following including at least one bolded option
 - Must be present for a 2 week period and represent a change from baseline
 - **Depressed Mood**
 - **Loss of interest/pleasure in all/almost all activities**
 - Significant *weight loss/gain* or appetite increase/*decrease*

- Insomnia or *hypersomnia*
 - *Psychomotor agitation* or retardation
 - Fatigue/Loss of energy
 - Worthlessness/Inappropriate guilt
 - *Inability to concentrate/indecisiveness*
 - *Suicidal ideation, obsession, or attempt*
- Different presentation in children- important to distinguish
 - Children may present with more of an activated presentation- see italicized above
 - Struggle to make decisions or focus for a significant period of time may be an indicator of depression in children
 - Important to differentiate from ADHD
 - Adolescents may present with more symptoms described as “borderline” and general lack of interest
- Differential
 - Bipolar disorder*
 - Most important differential as treatment may precipitate a manic episode in bipolar patients incorrectly treated for depression
 - Other psychiatric disorders
 - Drug of abuse or medication
 - More common in older patients
 - Life event (ie loss of loved one)
 - May precipitate a major depressive episode needing treatment but initially should be regarded as situational pending further evaluation
 - Medical condition induced depression
 - Cancer, hypo/hyperthyroid, stroke, central nervous system disorder
 - Medications of note *Key place for pharmacist led interventions
 - Antipsychotics
 - Beta Blockers
 - Contraceptives
 - Corticosteroids
 - Isotretinoin
- Clinical Characteristics
 - Co-morbid conditions
 - Often associated with other psychiatric disorders
 - Generalized anxiety disorder, eating disorders, obsessive compulsive disorder
 - Signs and symptoms
 - Outlined in diagnostic criteria
 - Laboratory values
 - Not of much value in diagnosis or treatment
 - Complications
 - Risk of prolonged course of disease, decreased quality of life, suicide attempts
- Goals of therapy
 - Selection of appropriate therapy including cognitive/psychological treatment
 - Resolution of signs and symptoms
 - Avoidance of adverse effects
 - Including suicidal ideation

- Long term remission
- Non-pharmacologic treatment
 - Plays a very important role in treatment
 - Psychotherapy should always be a component of childhood and adolescent treatment
 - Stand-alone in mild depression
 - Medication as adjunct in moderate to severe
 - Medication should never be used without concurrent psychotherapy
 - Studies overwhelming show benefit to this combination compared to medication alone
 - Cognitive Behavioral Therapy (CBT)
 - Interpersonal therapy
 - Increase coping skills
 - NOT been shown to be more effective than placebo in children
 - Newer studies may indicate that it may be as effective as CBT
- Pharmacologic Treatment
 - Potential option depending on severity and history
 - Indicators include:
 - Prior episode
 - Past pharmacologic treatment
 - Family history w/ significant response
 - Environmental causes addressed w/ no change
 - Failed psychotherapy
 - **Cannot simply use data in adults for treatment of children**
 - Neuronal pathways develop as we age
- Pharmacologic Treatment Options
 - TCAs previously used- not recommended
 - First line
 - Fluoxetine
 - Only agent with consistent data supporting a decrease in symptoms
 - Best evidence in younger children (2-11)
 - Citalopram
 - Sertraline
 - Other options
 - Escitalopram- indication for treatment of depression in children ≥ 12 yo
 - Venlafaxine ER
 - Lowest dose, moderate titration based on response and adverse effects, limited number of pills per prescription
- Agent Selection
 - Consider all relevant factors
 - Co-morbid conditions
 - Patient allergies or drug interactions
 - Cost
 - As in adult treatment, patient preference plays a role
 - Can be considered/honored if within our first line options
 - First line treatments should still be first line

- Patient preference for an agent that is not proven to be safe and effective in children is NOT a reason to use that agent
 - Crucial to assess parent preference as well
 - Compliance
- Fluoxetine- Prozac®
 - Approved ages: depression \geq 8 yo (limited data in 2-6 yo for anxiety)
 - Dosing:
 - Lower weight: 10mg PO daily, can increase to 20mg daily after several weeks; max is 20mg daily
 - Higher weight: 10-20 mg PO daily, may inc to 20mg daily after one week; max is 20mg daily
 - **Have seen doses up to 40mg in patients > 12 yo
 - Should be first agent considered -not necessarily first prescribed
 - Only noted agent w/ consistent effective results
 - Estimated 20-40% of patients will not be adequately treated
 - 2D6, 2C9, 2C19, 3A4 enzyme interactions, QT prolongation, anti-platelet, SIADH
- Fluoxetine Efficacy- Reported Data
 - Fluoxetine for Acute Treatment of Depression in Children and Adolescents Study
 - Three independent diagnostic interviews using two evaluation tools to diagnose nonpsychotic MDD
 - Children= 8 - <13 and adolescents= 13 - <18
 - Patients assessed at weeks -3, -1, 0, 1, 2, 3, 5, 7, 9
 - Exclusion: serious illness or other medical complications including bipolar or other psychological diagnoses
 - Inclusion: moderate depressive symptoms, able to swallow whole medication without difficulty
 - Methods
 - Placebo controlled, single blind, randomized
 - Multiple academic hospitals throughout the US
 - 110 in placebo group and 109 in fluoxetine group
 - Week 1 treatment= 10mg à Week 2-9= 20mg
 - Assess by trained investigators each week starting 3 weeks before treatment was initiated
 - "Remission" prospectively defined as endpoint Children's Depression Rating Scale- Revised (CDRS-R) score of \leq 28
 - A score of 30 is the cut off for depression using this scale
 - Results and Conclusions
 - Significantly greater improvement in CDRS-R scores in the treatment group
 - Defined as \geq 30% improvement in symptoms
 - No subgroup variations in results
 - "Significantly more fluoxetine- treated patients (41.3%) than placebo-treated patients (19.8%) met the prospectively defined criteria for remission ($p < .01$)...difference in the percentage of patients responding to treatment (fluoxetine: 65.1 %; placebo: 53.5%) was not significant ($p = .093$)"
 - Lack of significant results with other scoring systems

- Citalopram-Celexa™
 - Approved ages: Not FDA approved
 - Expert recommended dosing:
 - Children ≤ 11
 - 10mg/day, increase by 5mg/day every 2 weeks as needed
 - Usual range 20-40mg/day
 - Children ≥12
 - 20mg/day, increase by 10mg/day every 2 weeks as needed
 - Usual range 20-40mg/day
 - First line agent to be considered after fluoxetine
 - Option for patients who failed first agent or have initial aversion to fluoxetine
 - Similar interaction profile to fluoxetine; 3A4, 2C9, 2C19, QT prolongation, anti-platelet, SIADH

- Sertraline-Zoloft®
 - Approved ages: Not FDA approved, data for children 6-12 yo
 - Expert recommended dosing: 12.5-25mg daily , can increase by 25-50mg/day at a minimum of 7 day intervals; typical dose is around 1.6mg/kg/day at a range of 25-200 mg/day; max 200mg/day
 - Pediatric patients have a higher metabolism of sertraline- lower doses are still recommended
 - Drug interactions: 2C8, 2D6, 3A4, 1A2, QT prolongation, anti-platelet, SIADH

- Escitalopram- Lexapro®
 - Possible agent in resistant depression
 - Least data available in pediatric population
 - One RCT done in 2006
 - Did NOT demonstrate significant results when compared to placebo
 - More acceptable in older pediatric patients
 - Post-hoc analysis of adolescents (12-17) in 2006 trial did show significant improvement in CDRS-R
 - No significant side effects noted- headache and abdominal pain most common
 - Suicidal ideation still an issue
 - Further testing needed
 - Similar drug interaction profile

- Venlafaxine ER- Effexor XR®
 - Two RCTs to date
 - No statistical significant differences in CDRS-R scores between venlafaxine ER and placebo in either study
 - Possible benefit in adolescents (12-17) but no benefit seen with children (7-11)
 - Not studied in children younger than 7
 - Anorexia and abdominal pain most commonly reported side effects
 - Hostility and suicide-related events were seen in the treatment groups in comparison to the placebo group
 - Reserved for patients who fail fluoxetine and sertraline
 - Dosing: 37.5 mg/day x 1 week → 75 mg/day

- Have also seen higher doses in combination with lithium
- Other Options- FYI- Not recommended or proven to be effective
 - Desvenlafaxine- Pristiq*
 - *No generic available
 - Duloxetine- Cymbalta
 - Mirtazapine- Remeron
 - Bupropion- Wellbutrin
 - TCAs
 - Actually proven to be unsafe and ineffective
- Treatment Failure and Duration
 - Two different schools of thought in treatment duration
 - Guidelines dictate a duration of 8-12 weeks before terming a specific treatment as a failure
 - Newer data suggest that a more aggressive approach of only allowing 4-6 weeks before calling treatment with no change failure and attempting to change or modify treatment
 - If patient fails treatment with a first line agent, switch to another first line
 - If patient fails all first line - psychiatric consult
 - Multiple agents NOT indicated in children
 - Can be used in treatment resistant depression but this should be under the care of a trained specialist
 - Treatment should continue for at least 4-6 months after remission
 - Does NOT have to be lifelong
 - Should be warned about the risk of relapse and need for re-treatment
- Disease State Monitoring
 - Close monitoring in all cases
 - Black box warning for increased suicide risk
 - This population is particularly vulnerable
 - Weekly phone monitoring, regular visits to provider
 - SSRI- associated behavioral activation
 - Restlessness, hyperkinesia, agitation, hyperactivity
 - 2-3 times more prevalent in children
 - May be able to decrease risk with slower titration schedules (q 2-4 weeks)
 - Monitor weight and growth – concern for weight loss due to decreased appetite
- Suicidal Ideation
 - Clinical Response and Risk for Reported Suicidal Ideation in Pediatric Antidepressant Treatment
 - Meta-analysis of RCTs
 - 15 MDD (2910 participants), 6 OCD, 6 Non-OCD anxiety from 1988 to 2006
 - Increased risk for suicidal ideation or attempt
 - Applies to all trials for all indications
 - Highest rate of suicidality in placebo group w/ MDD trials
 - Overall NNH was 143, MDD NNH 112
 - Pooled risk of suicidal ideation/attempt in MDD trials was 3% in treatment vs. 2% in placebo (p=0.08) resulting in a difference of 1%
 - NNT was 10 for MDD (OCD=6, Non-OCD=3)

- While it was not significant, the highest risk and most modest benefit was in MDD trials
- Study Conclusions
 - Despite the increased risk, the risk vs. benefit picture is clearly in favor of the use of antidepressants in certain cases
- Considerations:
 - The trials included SSRIs and second generation agents
 - The average length of a trial was 8 weeks for major depressive disorder (MDD)
 - Most studies were multicenter; median number of sites was 21
 - For MDD trials, CDRS-R was used in 11/15 and CGI-I for response in 8/15
- Pediatric Medication Monitoring
 - Do NOT abruptly discontinue treatment
 - Certain side effects are more common in children than adults:
 - Other potential side effects
 - GI upset, HA, nervousness, restlessness, weight loss, rash, SIADH, bone fractures, CNS depression

In the case of JM, the physicians ruled her depression to be situational and decided it would be best that the patient not be placed on pharmacologic therapy but instead received continued counseling and close follow-up. As a new clinician, I do not necessarily agree with the designed care plan as I believe a suicide attempt after 6 months of CBT should be considered treatment failure and JM should be evaluated as a candidate for medical management, possibly with fluoxetine. However, much of pediatric medicine falls into a grey area and that is certainly the case for this particular patient.

Adequate treatment of pediatric depression is crucial to prevent adverse events later in life. When looking at an overall treatment course for a patient, cognitive therapy is always first line and pharmacologic treatment is not appropriate in all cases. However, if pharmacologic treatment is needed, fluoxetine is considered first line and the first agent that should be considered. Anytime medication is initiated, it should be in combination with cognitive therapy as this has been proven to be more effective than medication alone. Close monitoring is required in all cases and parents should be warned about suicidal ideation in a frank manner that will ensure everyone knows how

to best keep the child safe. Pediatric depression is a challenging disease state but basing treatment in evidenced based medicine and providing patient centered care can allow these children to go on to lead happy, healthy lives.

-A large part of this project for me was developing a lecture on this subject to teach to my classmates in order to prepare them to treat pediatric depression as clinicians in the future. In addition, I created the above, abbreviated and easy to use in practice guide to assist them in their clinical management in the future, as well as an assessment given at the conclusion of the lecture to ensure all important points were adequately covered. As this encompassed both my interest in pediatrics and academia, I was able to gain insights about this particular disease state, as well as the requirements to successfully lecture over a topic in a way that will assist future clinicians in the management of their patients.

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