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CLINICAL CASE ROUNDS

Psychopharmacological Approaches to a Case of Treatment Resistant Adolescent Depression

Editor's note: Welcome to the second "Psychopharmacology Challenge" from the Journal of the Canadian Academy of Child and Adolescent Psychiatry. Three clinicians (and their residents, in some cases) with expertise in pediatric psychopharmacology were asked to review the following patient vignette, and in 1000 words or less, describe the top three pharmacotherapy-related changes they would recommend for this patient, along with their clinical reasoning. Clinicians were asked to focus on psychopharmacology, but could also briefly indicate any suggested psychosocial intervention plans. For medication changes, clinicians were asked to include a recommended dosing titration plan [if applicable], and any additional testing they would order, including a recommended frequency of such testing. Clinicians were also asked to provide supporting literature citations for recommendations.

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The Case

DW is a 17-year-old female of Chinese descent, who weighs 73 kg with a height of 162 cm (BMI 27.8 kg/m^2, 92nd percentile for age). DW lives with her mother, father and 14-year-old brother. DW presents to the local child & adolescent mood and anxiety clinic with a chief complaint of ongoing unremitted symptoms of major depressive disorder, generalized anxiety disorder and social anxiety disorder. DW is currently taking venlafaxine 262.5 mg once daily in the morning and has been taking this dosage for the previous 12 weeks. DW also has current prescriptions for Alesse® (ethinyl estradiol 20 mcg/levonorgestrel 100 mcg per tablet) taken once daily on a cycle of daily for 12 weeks, followed by a 1 week break and then repeated, and lorazepam 1 mg twice daily as needed for anxiety (DW estimates she uses 4 doses per week).

Upon assessment, DW describes experiencing a partial response to venlafaxine, with improved mood, but persistent anhedonia and low appetite. DW goes to bed around 11 PM each night and reports not falling asleep until 1 AM. Once asleep, she sleeps for about 3 hours, and then finds she typically awakes at 4 AM and often arises and eats large quantities of carbohydrate-dense foods before falling back to sleep around 5 AM. She then reports she has trouble waking up to get ready for school at 7 AM. On school days, she reports taking a one-hour nap after school on most days and on weekends, she states she is exhausted and routinely sleeps in until noon. DW also reports that she sweats more than normal recently. DW reveals during the interview that she intermittently engages in non-suicidal self-injury in the form of superficial cutting on her arms (healed scars are evident on both of her arms, but there is no evidence of recent cutting). DW reports that she takes venlafaxine regularly because when she missed a dose once previously, she started to feel unwell later in the day with muscle aches and unusual sensations described as "nerve zaps". These symptoms resolved shortly after taking her usual venlafaxine dose the next morning. Upon completing an assessment of suicide risk, DW describes chronic feelings of wanting to end her life but denies any active plans and states she "wouldn't do that to my family." DW tells you she vapes nicotine on a daily basis, but denies use of alcohol or other substances. No significant trauma history was identified.

DW's most recent vital sign measurements by her primary care provider included a systolic blood pressure of 135/87 mm Hg with a resting heart rate of 97 bpm. No medical comorbidities were identified.

Table 1. Recent Laboratory Values

Hematology	Chemistry
WBC 4.9x10^9/L	Creatinine 54 µmol/L
(N=3.9-10.2x10^9)	(N=20-61 µmol/L)
Hgb 121 g/L	Sodium 137 mmol/L
(N=118-146 g/L)	(N=135-145 mmol/L)
MCV 83 fL	Potassium 4.4 mmol/L
(N=77-92 fL)	(N=3.5-5 mmol/L)
Neutrophils 2.5x10^9/L	Magnesium 0.83 mmol/L
(N=1.7-5x10^9/L)	(N=0.75-0.99 mmol/L)
Platelets 363x10^9/L	FBG 5.2 mmol/L
(N=180-440x10^9/L)	(N=3.5-5.9 mmol/L)
Ferritin 61 µg/L	TSH 2.91 mU/L
(N=13-66 µg/L)	(N=0.34-5.6 mU/L)
Vitamin B12 232 pmol/L	ECG NSR;
(N=118-700 pmol/L)	QTc interval = 442 msec

N: 'normal' reference range; ECG: electrocardiogram; FBG: fasting glucose; Hgb: hemoglobin; MCV: mean corpuscular volume; NSR = normal sinus rhythm; TSH: thyroid stimulating hormone; WBC: white blood cell count

Last year, DW saw a private psychologist who she described as using a cognitive behavioural therapy approach. DW recalls at least 10 visits over a period of 3-4 months. DW reports she found these sessions a little bit helpful but didn't have the motivation to complete most of the homework assignments or practice some of the recommended skills. She currently checks in with the mental health therapist that visits her school once monthly.

Prior medication trials

DW's medication trials prior to venlafaxine treatment were fluoxetine 10 mg daily for 1 year and sertraline 100 mg daily. Fluoxetine treatment was discontinued due to lack of efficacy following some initial benefit. Sertraline treatment was discontinued after 4 weeks of treatment due to intolerable gastrointestinal adverse effects (primarily gastritis and nausea).

DW's recent laboratory values are shown in Table 1.

Response #1

DW's presentation of major depressive disorder in adolescents (MDD-A) is complex; at the same time, many aspects of her profile are commonly observed in clinical practice. Our approach would be to start with a comprehensive psychiatric assessment and formulation. This can help guide treatment, particularly in more challenging clinical situations. We would pay close attention to any details that may be perpetuating DW's symptoms. For instance, we would want to know the extent of impairment related to her anxiety symptoms. It is possible that anxiety is leading to avoidance of social interactions, leading to isolation and worsening mood. Similarly, we would want to know the context of her lorazepam use, as it is likely that it is being used to avoid distress, which only perpetuates anxiety through negative reinforcement patterns. Comorbidities could also be perpetuating her depression, and so would warrant a careful psychiatric review of symptoms. We would specifically ask about symptoms of hypo/mania, personality disorders, and eating disorders. If she is distressed or impaired by her current eating after bedtime, then she would meet criteria for night eating syndrome, a subtype of other specified feeding and eating disorders described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) (1). It would be essential to assess for commonly co-occurring symptoms such as discomfort with one's body shape, compensatory behaviour (e.g. fasting, purging, excessive exercise), or change in physical health status (e.g. weight loss/gain, syncopal episodes, fatigue). Given the report of low appetite, we would wonder about late night binges impairing her normal hunger cues (2). Finally, in terms of clarifying diagnosis, we would take a thorough social history. Any stressors in school, friends, or family life would be very relevant.

With respect to the venlafaxine, we would discuss the risks and benefits of continued use. Notably, venlafaxine has a recommendation for third line use in CANMAT guidelines, after fluoxetine, sertraline, escitalopram and citalopram (3). Conversely, NICE guidelines explicitly recommend against the use of venlafaxine (4). These later recommendations are consistent with findings from at least two RCTs for the treatment of MDD-A where venlafaxine did not separate from placebo on depression symptom severity outcome; moreover, its metabolite, desvenlafaxine did not separate from placebo in a third RCT (5,6). Similarly, a recent Cochrane meta-analysis showed that venlafaxine had a slightly higher rate of suicide-related outcomes and less evidence of effectiveness compared to fluoxetine, sertraline, escitalopram and duloxetine (7). Venlafaxine in adolescents was not found to be any more or less effective as an SSRI in treating depressive symptoms that have not responded to an initial SSRI; and was associated with greater adverse effects compared to switching to a second SSRI (8).

In DW's case, venlafaxine may be contributing to her mildly elevated blood pressure/resting heart rate, sweating,

and her risk of non-suicidal self-injury. Additionally, she is likely experiencing antidepressant discontinuation syndrome when she misses a dose, as represented by "nerve zaps" – paresthesia-like symptoms often experienced in the scalp. These adverse effects may be worsened by the fact that she is on a supratherapeutic dose (a maximum of 225 mg daily according to product monograph) (9). Meanwhile, she is not experiencing remission in her depressive symptoms, so increasing the dose or continuing status quo are not options. Therefore, balancing DW's personal experience with recommendations from guidelines, we would advise her to discontinue venlafaxine and switch to a different antidepressant. We would slowly taper the venlafaxine by 37.5 mg per week until discontinued. Starting the next antidepressant (see below) when she is at lower doses (e.g. 37.5-75 mg daily) may theoretically help alleviate withdrawal symptoms at the tail end of the taper.

Our first choice for an alternative antidepressant is to try fluoxetine again. Her previous trial was deemed ineffective, however she was at a subtherapeutic dose of 10 mg. Our target dose for a 17 year old patient is 20-60 mg daily. We would start 10 mg daily of fluoxetine for 1 week, then increase to 20 mg daily thereafter for at least 3 weeks (4). If needed, fluoxetine can be increased by 10-20 mg increments every 4-6 weeks, though, to our knowledge, the evidence for higher doses is limited to one small trial (10).

Fluoxetine has the added benefit of treating DW's comorbidities. According to the Canadian Anxiety Guidelines, it is recommended as the first choice in treatment of both generalized anxiety and social anxiety disorder in adolescents (Level 2 and 1 evidence respectively) (11). For contrast, we note that the NICE guideline recommendation for social anxiety advises "Do not routinely offer pharmacological interventions to treat social anxiety disorder in children and young people" (12). Fluoxetine is also recommended for the treatment of bulimia nervosa in adolescents (13), which could theoretically help DW with her late night "binges". Night eating syndrome may be treated with SSRIs in general, adding credence to a retrial of fluoxetine (2).

If fluoxetine remains ineffective at higher doses, we would clarify how the previous trial of sertraline was started. Side effects may be more likely if titration was too fast. As sertraline has substantial evidence for treating anxiety (14), this may be a second-line option if DW is agreeable to a rechallenge. Then we would consider either escitalopram or duloxetine as next steps. We would start escitalopram at 5-10 mg daily and increase to 20 mg daily after 4-6 weeks if necessary. Two RCTs support the use of escitalopram in MDD-A (15,16). Alternatively, we would start duloxetine at 30 mg daily and increase by 30 mg increments every 2-4 weeks. Interestingly, there are 2 RCTs on duloxetine for treatment of MDD-A that did not separate from placebo (17,18); however a recent network meta-analysis did show some signal of efficacy (7).

In regards to DW's other medication, we would recommend discontinuing lorazepam. It can be replaced with distress tolerance skills, learned through psychosocial approaches. The evidence regarding oral contraceptives and mood has been conflicting, however a recent large registry-based cohort study found that there was no association between oral contraceptives and depression, including among youth aged 15-19 (19). Oral contraceptives containing drospirenone have evidence for treating premenstrual dysphoric disorder, so could be considered in collaboration with her family doctor (20).

Finally, psychosocial interventions would also be helpful for DW. According to NICE guidelines, if individual cognitive behavioural therapy is unsuccessful in youth aged 12-18, then the following options are recommended: interpersonal therapy- adolescent, family therapy, brief psychosocial therapy or psychodynamic psychotherapy (4). DW's engagement with non-suicidal self-injurious behaviour is concerning and a risk marker for poor outcomes (21). There is evidence that dialectical behaviour therapy (DBT) decreases self-harm and suicide attempts; however, the comprehensive DBT programs tested in two RCTs of adolescent samples is not always readily available (22,23).

To summarize, we would recommend slowly tapering venlafaxine, discontinuing lorazepam, and re-trialing fluoxetine in order to better treat DW's MDD. Based on clinical experience, many young people with DW's profile can obtain a complete recovery.

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Response #2

This case illustrates a frequently encountered clinical conundrum of a youth with treatment resistant depression and multiple comorbidities. Part of the challenge lies in deciding where to begin. While psychosocial interventions, such as family therapy and interpersonal therapy, are core to management (1,2) and should be encouraged in a case like this, there are multiple pathways of intervention from a psychopharmacologic standpoint. Potential clinical targets might include residual symptoms of major depressive disorder (MDD), comorbid anxiety disorders, comorbid sleep disorders, self-harming behaviours, bingeing episodes, medication and substance-related side effects, and comorbid nicotine use. Prioritizing treatment targets involves a process of reciprocal and shared decision making between patient, family, and clinician; considers functional impact and/or symptom severity; considers other diagnostic possibilities and formulations; and potentially incorporates theoretical elements from other approaches to complex clinical scenarios (3). Borrowing from structural elements of dialectical behavioural therapy (4), clinicians might begin with life threatening issues before proceeding to therapy interfering and quality of life interfering issues (5).

While it is up for debate where to categorize each of the aforementioned areas of clinical focus, one possible algorithmic approach to DW's situation is 1) to reduce major risks factors for suicide and self-harm, 2) to reduce factors that significantly impact adherence and long-term acceptability of medication, and 3) to address symptoms and issues that impact DW's quality of life. The clinical rationale for such an approach is to focus treatment and to avoid making too many pharmacologic changes all at once, while also providing some scaffolding around how to proceed when faced with overwhelming complexity. At the same time, one must be careful in applying such an approach beyond the scope of its initial intended use.

While DW currently presents with no active suicide plans, it is important to address her sleep as a vulnerability factor for suicide (5,6). Targeting her sleep would also be important given the bidirectional and complex relationship between sleep disorders and MDD (7,8). Behavioural and non-pharmacologic approaches remain the mainstay of treatment, but sedating medications can play a role in short-term treatment (4 weeks duration or less) by reducing sleep onset latency (7,9,10). Decisions might be guided by a more thorough sleep assessment as well as consideration of common causal and developmental features of sleep in youth (7,11). For DW, possible clinical considerations include insomnia (with both prolonged sleep onset latency and early morning awakening), sleep phase delay typical of adolescence, nicotine use, and daytime napping. Treatment suggestions could include the following:

Melatonin 1-12 mg in the evening. If there is an element of sleep phase delay, Pelayo and Yuen suggest administering exogenous melatonin 1.5-6 hours before dim light melatonin onset (DLMO) to more effectively advance circadian timing (11). Of note, both American and European guidelines for chronic insomnia in adults do not recommend the use of melatonin (9,10).

Mirtazapine 3.75–15 mg at bedtime. The primary rationale for mirtazapine is to reduce sleep latency by utilizing its sedating qualities at lower doses (9,10). Mirtazapine might also be used as an adjunctive agent to address the partial response to venlafaxine, though such a clinical decision would be informed by evidence in adult populations and not children and youth (12,13). The duration of treatment on mirtazapine would be dictated by its intended use: as a sleep aid (4 weeks) vs MDD adjunctive agent (at least 6-12 months) (1). Monitoring would include a repeat ECG, after the addition of mirtazapine, to monitor DW's QTc interval (13).

With regards to therapy or treatment interfering factors, it is important to explore DW's perception of the tolerability and acceptability of venlafaxine, balanced with her partial response on the medication. While there is limited evidence for doses up to 375 mg daily in severely depressed inpatients, recommended doses are generally up to 225 mg daily (13). If the increase to 262.5 mg daily has had very minimal perceived benefit, DW might consider lowering the dose, which hopefully minimizes some of the potential side effects such as increased sweating and elevated QTc interval. Unfortunately, this dose decrease might have little impact on the withdrawal symptoms that she experiences with missed doses. There also remains the question of what to do about the residual symptoms of depression. While reducing polypharmacy is ideal, this needs to be balanced with the fact that DW has tried at least two other antidepressants and has had partial benefit from venlafaxine (12). One possible adjunctive treatment is omega-3 fatty acids at doses of 1-4 grams daily (1-2 g eicosapentaenoic acid (EPA) and 1-2 g of docosahexaenoic acid (DHA)) (14). Omega-3 fatty acids have a relatively low side effect burden, which might positively impact treatment adherence. Ongoing monitoring would ideally occur on a weekly basis for the first month of treatment, then spaced out over time (1,13).

On a final note, the therapeutic potential of medications might be bolstered by a critical exploration of the intra and interpersonal aspects of prescribing. This could include Schiff et al's "principles of conservative prescribing" (15), or involve an evocation of themes relevant to the depressed youth's experience with taking prescribed medications. Medications and multiple trials can influence or impact one's sense of autonomy and agency, or have implications on the subjective severity and intractability of an illness (16). It would be important to acknowledge DW's expectations and hopes around medication, and to discuss the possible limitations of pharmacotherapy, especially as monotherapy for treatment resistant depression. There is also much to examine from a psychodynamic, behavioural, family systems, and sociocultural lens. This might involve looking at the transferential-countertransferential and/or re-enactment potentials of prescribing for treatment resistance; the role of behavioural change principles in medication adherence; or the symbolic, social and cultural values ascribed to particular medications by the clinician, the patient, the family, and the sociocultural and institutional contexts within which they exist (3,5,16–19).

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Response #3

This case exemplifies the importance and limitations of evidence based interventions. In this commentary, we will focus on the psychopharmacology aspects of the case. Yet, we cannot overstate the importance of a comprehensive treatment plan that includes psychoeducation, complementary and alternative options, as well as psychotherapy, and lifestyle modifications including physical activity, healthy diet, and sleep hygiene.

In choosing an optimal psychopharmacological approach, it is important to consider our patient's factors, including their symptom profile, comorbid conditions, response and side effects to previous antidepressants, and personal preference. We should also consider medication factors including tolerability, interactions with other medications and supplements, simplicity of use, and medication coverage (1).

The possible options for this case include: adding an adjunctive medication, switching to an alternative agent, and/or psychosocial treatments. Utilizing measurement based care will help objectively guide these treatment decisions and monitor the outcomes.

After discussing the different options with the patient and her family, we could decide to use an adjunct second

generation antipsychotic medication, such as quetiapine. Quetiapine could help boost their initial response to venlafaxine, and be a quicker solution to some of the patient's concerns. Further, it has evidence for improvement of anxiety and depressive symptoms, as well as the potential to improve appetite and sleep (2). We would recommend initiating quetiapine at 12.5 to 25 mg daily, and increasing weekly until reaching adequate clinical response, hence a need for frequent monitoring. Although there are no clear guidelines for optimal augmentation dosing for young people, CANMAT guidelines for the adult population recommend a target dose between 150–300 mg daily. The use of quetiapine requires baseline and routine metabolic monitoring including height, weight, waist circumference, blood pressure, and blood work investigations following CAMESA guidelines (3). Notable drawbacks for quetiapine include its well known metabolic side-effects, for which youth are at an increased risk (4). Another factor to consider is the additional cardiac side effects including QTc interval prolongation associated with polypharmacy (5). These side effects could lead to long-term concerns, and prevent us from recommending augmentation with quetiapine as our preferred treatment option.

Alternatively, the patient could be switched to a different medication. CANMAT guidelines would support this approach because the patient has only been trialed on one prior antidepressant and at a subtherapeutic dose of only 10 mg daily of fluoxetine. Although venlafaxine has evidence for efficacy and safety use in young people, adverse side effects prevent it from being a first line option in youth with depression (6). Further, the patient has not reached full remission despite exceeding the maximum dose of 225 mg daily recommended according to CANMAT and the TORDIA study. Of the three common SSRIs often used in young people (fluoxetine, sertraline and escitalopram), fluoxetine would be our preferred agent because it has the most evidence to support efficacy for pediatric MDD (level 1 CANMAT) (1). Additionally, the patient had an initial positive response to fluoxetine, and we know that early improvement positively correlates with later response and remission (7). The previous trial did not afford adequate time or therapeutic dose. Moreover, the long half-life of fluoxetine and it metabolite desmethyl-fluoxetine will minimize the risk of withdrawal symptoms experienced in shorter acting antidepressants such as venlafaxine or paroxetine. This is particularly important in young people whom tend to struggle with poor adherence (8).

A cross-tapering can be performed, keeping in mind this strategy is not an exact science. Since the current dose of venlafaxine is high at 262.5 mg daily, we would start by decreasing the dose of venlafaxine either by half or to 150 mg daily depending on the pills that patient has. This will reduce the risk of serotoninergic syndrome; after a few days a small dose of fluoxetine 10 mg daily can be started and will help minimize venlafaxine's discontinuation symptoms. After a week or two depending on tolerability, venlafaxine will be fully discontinued and fluoxetine can then be increased to 20 mg daily. The target dose range for depression using fluoxetine in young people is between 20-60 mg daily based on clinical response, and tolerability. The dose increments should be done based on tolerability and clinical response, allowing several weeks in between to observe the antidepressant response. During the transition, although it may be tempting to maintain dual treatment if symptoms improve, a complete cross over to fluoxetine monotherapy will help to reduce the risk of adverse reactions and likely improve adherence. While making this change, the patient should be carefully monitored for both increased thoughts of self-harm and suicide and serotonin syndrome symptoms (1,6).

In addition to the above covered possible interventions, it will be important to rule out hyperthyroidism and diabetes with testing for TSH and hemoglobin A1c levels. This is based on the excessive sweating that the patient is experiencing, and these two conditions are commonly associated with the onset of depression.

We also want to emphasize the importance of exercise, given the patient's BMI and the substantial evidence supporting the benefits of physical activity in mild to moderate depression. Physical exercise is an effective intervention for depression and can be used as monotherapy in mild to moderate depression, or as an adjunct treatment in combination with antidepressants for moderate to severe depression (1,9).

We would like to close with highlighting that CANMAT guidelines and the main clinical CAP trials continue to emphasize and prioritize the use of cognitive behavioral therapy in the treatment of major depressive disorder in young people (1,5). Being in line with new evidence requires us to continue to emphasize psychotherapy's efficacy and in some cases superiority to pharmacological treatments (10).

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