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## *Advanced Pediatric Psychopharmacology*

# Renal Failure in a Depressed Adolescent on Escitalopram

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Escitalopram (Lexapro) is the most recent selective serotonin reuptake inhibitor (SSRI) approved by the United States Food and Drug Administration (FDA) in 2002 for treatment of adults with major depressive disorder, social anxiety disorder, and generalized anxiety disorder. To date, it has not been approved for use in children or adolescents, as data regarding its safety and efficacy in youths is insufficient. However, it is often prescribed off label in this population for similar indications.

This report describes a 17-year-old girl with a history of major depressive disorder and congenital deformity of the upper limbs who developed allergic interstitial nephritis and acute renal failure during a course of treatment with escitalopram.

### Chief Complaint and Presenting Problem

R. was a 17-year-old Caucasian girl and junior in high school who lived with her parents and 13-year-old sister. She was transferred from another hospital with acute renal failure possibly secondary to escitalopram use, which she had taken for treatment of major depressive disorder. She was subsequently referred to the inpatient consultation team for medication evaluation and management.

### History of Present Illness

R. had a history of mood and behavioral problems with onset over a year ago when she was 16 years of age. She was described as often irritable, snapping, talking back, and oppositional. She experienced a period of time when her peers teased her about her congenital deformity. She began to have difficulty maintaining her grades in school. She had crying spells, negative thoughts about herself, and feelings of worthlessness. She reported that she did not feel like she wanted to live any more. On one occasion, she scratched her wrists with a pin, and on another occasion, with a knife; these self-injurious behaviors were reportedly suggested to her by a friend. She reported feeling better after scratching and cutting herself and denied any intention to die.

### Past Psychiatric History

R. started psychotherapy with a psychologist for depression when she was approximately 16 years old. Escitalopram 10 mg was subsequently initiated by her primary care physician. She continued on this dose for 6 months without any adverse effects. The dose was then increased to 20 mg when it became apparent that her depression was not well controlled. After four months at 20 mg, there was a significant improvement as a result of therapy and medication, so her mother stopped the medication for a week. The patient was also discharged from the therapist's care due to her symptomatic improvement.

When R. returned for follow-up to the primary care physician, it was recommended that she continue taking medication, as it was felt that the remission of her depressive symptoms was too recent to be likely to be sustained. The recommendation was to continue the escitalopram for the next year, her junior year in high school, and then discontinue it.

There was no previous history of psychiatric treatment or treatment with any other psychotropic medications.

### Developmental History

R. was the product of a full term, uncomplicated pregnancy and vaginal delivery. She was born with a congenital defect of bilateral hemimelia of her upper limbs. Her developmental milestones were on target except for walking, which she did not achieve until 18 months, as she was unable to use her hands for support.

### Educational History

R. was an eleventh grade student at a public high school. Her grades averaged Cs and Ds. She liked math but not science. She had an Individualized Educational Plan for her disability which provides accommodations.

### Social History

R. lived with her biological parents and 13-year-old sister. She reported that she felt her parents were harsh with her, especially her father. She denied any abuse or trauma. She had a few close friends at school. She had experienced teasing by her peers about her disability. She had a boyfriend who her mother approved.

### Family History

A.'s mother reported that she had taken alprazolam for anxiety in the past. There was no family history of renal disease or other psychiatric disorders.

### Medical History

R. had a past history of polyuria, which was never investigated, and thus there was no known diagnosis of renal problems. She also had used an unknown dose of ibuprofen 3-4 days per month for menstrual cramps.

### Mental Status Examination

R. was wearing a bright pink dressing gown over her clothes, which covered her arms. She was fairly pleasant, and co-operative. Rapport was established and eye contact was maintained. She was able to use a pincer-like grip and was able to perform tasks such as unscrewing a bottle cap.

Her psychomotor activity level was appropriate to the situation. Her speech and language was notable for normal pressure and volume. Her affect was appropriate to the situation and revealed a fairly good range. Her mood was euthymic. Her thought process and form were coherent and goal-directed.

R. denied any current negative thoughts about herself or the future. She reported that she was satisfied with the care she had received and stated that this experience made her more appreciative of everything she has, including her family. She described feeling hopeful and wanting to live her life, so that she could become a psychologist and have a baby. She denied any current suicidal ideation, intent, or plan. She did report that she believed her parents were unreasonable at times. She stated that therapy has helped her put things in perspective and allowed her to better appreciate them.

R. was alert and oriented with intact attention/concentration and recent and remote memory. Her fund of knowledge was average, and her insight and judgment were fair.

### Clinical Course

Two to three weeks after restarting escitalopram, R. began to have nausea and vomiting followed by abdominal pain and diarrhea. Over the next 3 weeks, she was treated symptomatically with metoclopramide, which provided temporary relief, but the nausea, vomiting, and pain continued to recur. She also had one episode of dark black stools. She denied both having overdosed on the medication and taking extra pills. During that time, she was also given a prescription for alprazolam 0.5 mg twice daily as needed, for anxiety relating to her medical problems, which she took for a total of 6 times over 1 month.

She was subsequently taken to a local hospital where she was diagnosed with acute renal failure. Her creatinine at that time was 4.9 mg/dl (normal range: 0.5–1 mg/dL) and her glomerular filtration rate was 12 (normal range: 60–80 $mg/mL/m^{2)}$. No specific cause for renal failure was identified.

A renal ultrasound was performed, which demonstrated normal kidney appearance, normal flow on color Dopplers, and no collecting system dilatation. Renal biopsy was inconclusive, as the sample was inadequate. R. was also found to be anemic, but no gastrointestinal source for bleeding was identified.

Escitalopram was discontinued 4 days after the diagnosis of renal failure was made. The workup revealed moderate eosinophiluria and eosinophilia, which was suggestive of drug-induced allergic interstitial nephritis. At time of discharge one week later, her creatinine had reduced to 2.1 mg/dL, and her symptoms had improved.

### Brief Formulation

In summary, R. is a 17-year-old Caucasian girl with a history of major depressive disorder treated with a 10 month course of escitalopram. She presented for admission with nausea, vomiting, and abdominal pain consistent with acute renal failure, possibly due to the escitalopram. Her renal function improved with discontinuation of the medication.

From the biological/medical perspective, given her past history, escitalopram might have worsened a previously existing, undiagnosed renal disorder, either by itself or in combination with the nonsteroidal antiinflammatory agent.

There is evidence that R.'s depression responded well to treatment with escitalopram and psychotherapy without any adverse events prior to the onset of acute renal failure. In addition, R. may have had a diathesis for affective illness, given the family history of anxiety on the maternal pedigree. Furthermore, R.'s physical disability appeared to be an underlying issue for which she felt vulnerable, and had not yet been able to successfully deal with this with her peers, which may have rendered her more vulnerable to low self esteem and negative self image. From a psychological perspective, R. appeared to be dealing with typical adolescent developmental issues with her parents, but did experience them overall as supportive and involved. Socially, on the positive side, she had been able to achieve a relationship with a boyfriend, despite her difficulties, and she had plans for the future.

### Multiaxial Diagnoses

Axis I: Major depressive disorder, single, in full remission
Axis II: Deferred; rule out borderline features
Axis III: Acute allergic interstitial nephritis
Acute renal failure, possibly secondary to escitalopram
Hemimelia.
Axis IV: Interpersonal problems with peers.
Axis V: Current Global Assessment of Functioning Score: 60

## Discussion

Although there is no conclusive evidence for the causative role of escitalopram in renal failure in this patient, this case brings up several important issues in clinical pediatric psychopharmacology practice, including choice of medication, and the role of previous medical history.

To date, there is only one controlled trial of escitalopram in the treatment of major depressive disorder in children and adolescents (Wagner et al. 2006). There are no formally established guidelines for dosing or duration for escitalopram in youth. Escitalopram is recommended as a second-line agent as monotherapy for treatment-resistant depression in the Texas Childhood Medication Algorithm, due to the paucity of controlled trials in adolescents. SSRIs for which there is an evidence base for treatment of major depression in youth include fluoxetine, citalopram and sertraline (Hughes et al. 2007, Emslie et al. 2002, Wagner et al. 2004, Wagner et al. 2003, March et al. 2004).

In the absence of level A (randomized controlled trial) data, many psychiatrists prescribe antidepressants for children and adolescents that have been beneficial to their first degree relatives; however, this appears does appear to have been the case with R. Thus, one could question the use of this agent as a first-line treatment when the extant evidence base is stronger for several of the older agents.

With regard to pharmacokinetics, the difference in the plasma concentrations of a single dose of escitalopram between healthy adolescents and adults is not significant (Rao 2007). It is primarily metabolized in the liver by enzymes CYP3A4 and 2C19 with 8% of drug excreted unchanged in urine. The most common adverse effects reported in adults with escitalopram are nausea, insomnia, ejaculation disorder, diarrhea, fatigue, dry mouth, and sweating.

The single controlled trial of escitalopram in youth was an 8-week double-blind study in adolescents with depression; results revealed a high incidence of headache and abdominal pain(Wagner et al. 2006). In a 10-week open label trial in children with Pervasive Developmental Disorder, the most common side-effects reported were irritability and hyperactivity (Owley et al. 2005). In a case series of 5 adolescents treated with escitalopram for major depression, there were no reports of significant adverse events (Schaller and Rawlings 2005.

Most depressive illness in youth is usually of long duration, lasting months to years. However, there is little evidence base for long-term treatment greater than 8–12 weeks with any of the SSRIs; there is a report of long-term use of citalopram up to one year (Thomsen et al. 2001.

Taken together, we cannot be sure that the drug, dose or duration of treatment with escitalopram was causative of her acute renal failure; both her past history of polyuria and chronic use of ibuprofen could have rendered her vulnerable to development of renal problems, independent of escitalopram.

Drugs associated with allergic interstitial nephritis include antibiotics, anticonvulsants, and diuretics. Though rare, nonsteroidal anti-inflammatory drugs (NSAIDs have also been associated with allergic nephritis and renal failure (Agarwal et al. 2003).

In practice, patients often use NSAIDs without the clinician's knowledge and do not volunteer the information unless specifically asked. NSAIDs are not benign, and, in combination with SSRIs, may increase the risk of bleeding. Interestingly, R. did present with anemia, although no source of bleeding or overt cause was determined. A more complete workup would be indicated.

Our conclusion is that escitalopram should be used with caution in children and adolescents. First-line treatment with one of the SSRIs with an established evidence base of safety and tolerability is indicated, such as fluoxetine, sertraline, and citalopram. The clinician should be vigilant to the possibility of new onset of any medical complaints during treatment, particularly until further data is compiled regarding its safety and efficacy in children and adolescents.

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