THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter

February 2015 Volume 5, Issue 1

Evaluation of High Dose SSRI Initiation in Pediatrics and Young Adults

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There is conflicting evidence in the literature regarding initiation of selective serotonin reuptake inhibitors (SSRIs) and the increase of new-onset of deliberate self-harm (DSH) thoughts and behaviors, or suicidality. In 2004, the Food and Drug Administration (FDA) added a black box warning to the labels of many antidepressants in response to case reports[1] describing increased risk of suicidal thinking and behavior among pediatric patients taking SSRIs.[2] However, other studies disagree with this claim, and the FDA warning led to fewer visits and prescriptions written for depression. A meta-analysis conducted by the FDA in 2006 and a more recent Cochrane systematic review further established this relationship, reporting a statistically significant, moderate increase in suicidality among users of SSRIs aged 24 years and younger.[3] However, until very recently, no study had been conducted to explore an association between DSH and antidepressant dose.[4] This newsletter will summarize recent literature describing dose-related effects of SSRIs in pediatric patients as well as a recent drug use evaluation in the Oregon Medicaid population. Recommendations for SSRIs in pediatric patients, approved by the Oregon Pharmacy and Therapeutics (P&T) Committee in response to these study results, will also be described.

Pediatrics and SSRIs

Miller et al. recently published the results of a large propensity score-matched, retrospective cohort study that examined how antidepressant dose at initiation of therapy affected resultant risk of DSH.[4] This study involved 162,625 patients aged 10-64 years who had been diagnosed with depression and were initiating one of three SSRIs (citalopram, fluoxetine, or sertraline). Doses were categorized as modal, lower than modal, or higher than modal relative to the overall distribution of doses prescribed for study participants. Modal doses for each SSRI included in this study are defined in Table 1. Analyses were limited to patients prescribed modal (n=32,504) or higher than modal doses (n=7117).

Table 1. Modal Doses of Antidepressants[4]

Citalopram	20 mg/day
Sertraline	50 mg/day
Fluoxetine	20 mg/day

Overall, 13.1% of patients aged 10-24 years were initiated on a higher than modal SSRI dose. A total of 142 of the 21,305 modal or high dose participants aged 10-24 years engaged in DSH in the year after starting treatment (68 of whom were prescribed a modal dose and 74 a higher than modal dose). Among patients in this age group, those initiated on higher than modal SSRI doses were significantly more likely to engage in DSH than were their counterparts initiated on modal doses (HR, 2.2; 95% CI, 1.6-3.0). For every 1,000 patients in this age group initiating high dose SSRIs, researchers found approximately 7 more instances of DSH over the first 90 days of treatment, as compared to those initiating with a modal dose (NNH=136). No statistically significant relationship between dose and DSH was noted for patients aged 25-64 years. Miller concluded that these results provide strong evidence against initiating high-dose antidepressant therapy in adolescents and young adults with depression.[4] In addition, very limited evidence exists to demonstrate that greater antidepressant doses produce greater relief of depressive symptoms.[5-8] For instance, one meta-analysis of 33 relevant studies reported that higher doses were not accompanied by increased efficacy, and that adverse events significantly increased with dose.[7]

Drug Use Evaluation

Due to the results of the Miller study, a drug use evaluation was subsequently undertaken to describe the frequency of high dose SSRI initiation in Oregon Medicaid patients under 25 years of age.[9] A cross-sectional study was performed; patients were included if they had a paid claim for a SSRI between April 1, 2013 and March 31, 2014. Patients younger than 5 years (n=19) or those on fluvoxamine (n=31) or paroxetine CR (n=10) were excluded due to small numbers coupled with the lack of definitive dosing recommendations for these treatments.

There were 4,879 patients newly-initiated on one of five SSRIs (citalopram, escitalopram, fluoxetine, immediate-release paroxetine, or sertraline). As in Miller's study, doses were categorized as modal, lower than modal, or higher than modal. However, unlike Miller's paper, which established a single modal dose for each SSRI, modal doses in this study were determined for multiple age groups (5-9, 10-15, 16-19, and 20-24 years). Age-specific and pooled modal doses for SSRIs included in this study are defined in Table 2.

Table 2. Drug Use Evaluation Modal Doses of Antidepressants[9]

SSRI	Age-specific modal dose (mg/day)				Pooled modal dose (mg)
	Age range (years)				
	5-9	10-15	16-19	20-24	
Citalopram	10	10	20	20	20
Escitalopram	5	10	10	10	10
Fluoxetine	10	10	10	20	10
Paroxetine (immediate release)	10	10	20	20	20
Sertraline	25	25	50	50	50

This drug use evaluation reported that 27.0% (n=1301) of patients under age 25 years were initiated on a SSRI above the modal dose, thus increasing these patients' risk of DSH without necessarily increasing therapeutic efficacy. Patients aged 10-15 years were most likely to have been initiated above a modal dose (53.8%), as were patients with a diagnosis of MDD or depression (35.0%). This is especially concerning, because the Miller study, which reported a dose-dependent increase in risk of DSH, focused specifically on MDD patients.

Fluoxetine, sertraline, and citalopram were the most frequent SSRIs initiated (86.9%). Fluoxetine was both the most commonly-prescribed SSRI (33.7%) and the most likely to have been initiated above modal dose (47.2%). There are several possible explanations for this finding; among them, that a lower pooled modal fluoxetine dose was used in this study than was used by Miller (10 mg, as compared to 20 mg, respectively), which could infer differences in our population compared to the population evaluated in the Miller study. Although a fluoxetine dose of 10 mg daily is on the lower side of the recommended starting dose range (Table 3), it is not uncommon for transition age adults (16-25 years) to be initiated on higher doses (20 mg), particularly those with severe depression, due the prolonged half-life of fluoxetine.[9] The use of the lower pooled modal dose in the adolescent age

groups could have led to an increased number of patients categorized as initiated above modal dose. In addition, fluoxetine is first line therapy for depression, has a longer history of use, is FDA approved for pediatric patients and has the most supporting evidence for treatment of MDD and additional indications. Therefore, practitioners may be more comfortable prescribing fluoxetine at higher doses.

It is also important to make note that paroxetine has no FDA approved pediatric uses and based on expert opinion, can cause significant agitation and suicidal ideation.[13] Cessation can also be very different due to withdrawal issues. It may be prudent for only experienced pediatric mental health providers to use initiate paroxetine in children and adolescents. Although rarely prescribed, fluvoxamine has similar safety concerns.

Table 3. Recommended Initial and Maximum Dose in Children and Adolescents[10-12]

	Recommended Initial Dose* (mg)	Recommended Maximum Dose* (mg)
Citalopram	10-20	40
Escitalopram	5-10	20
Fluoxetine	5-20	20-80
Paroxetine** (immediate release)	10-20	50
Sertraline	12.5-50	200

*Doses for MDD or depression were used if listed and other indication doses were used if no MDD or depression dose was available
**No FDA approved indication for pediatric use

Conclusion and Implications to practice

Results of this drug use evaluation identified 27% of Oregon Medicaid patients aged 5 to 24 years were initiated on high-dose SSRI therapy during the study period. The association between SSRI use and increased risk of DSH remains controversial, and the potential DSH risk is quite small compared to the risks of untreated MDD.[9] Recent meta-analyses, cited by Miller, have demonstrated that the antidepressant dose is generally not related to its therapeutic efficacy.[4-8] Therefore, Miller proposes that limiting antidepressant dose at initiation is a means by which MDD may be treated, while antidepressant-associated increases in DSH risk may be minimized.[4]

On the basis of the study results described above, and to avoid exposing pediatric, adolescent, and young adult patients to undue risk of self-harm, the Oregon P&T Committee has approved the following recommendations,[9] which will be implemented in April of this year.

1. Initiate a maximum dose prior authorization for patients less than 25 years starting SSRIs (i.e. no prior antidepressant claim in the previous 102 days). Set the dose at the age-specific modal doses used in the drug use evaluation study (Table 2) except increase the fluoxetine dose to 20 mg for 16-19 year olds.

2. Exclude child psychiatrists from the prior authorization requirement.

3. Consider age edit to restrict use of paroxetine and fluvoxamine to adults (>18 years) per expert opinion.

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