CELEXA® (CITALOPRAM) UTILIZATION AND DOSING MANAGEMENT

BACKGROUND

In May 2007, the FDA issued a notice that the agency was updating the black box warning for antidepressants to include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months).[1] FDA's black box warning in Celexa's package insert is shown below.

> **Suicidality and Antidepressant Drugs**
>
> **Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Celexa or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Celexa is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)**

Also in 2007, a study that was partially funded by the National Institute of Mental Health was published reporting results of a comprehensive review of pediatric clinical trials conducted between 1988 and 2006.[2] The study suggested that the benefits of antidepressant medications likely outweigh their risks to children and adolescents with major depression and anxiety disorders. More recent studies have supported these conclusions. Antidepressant-induced suicidality appears to be an uncommon occurrence but also a legitimate phenomenon that needs to be monitored.[3,4]

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1 U.S. Food and Drug Administration. FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications. May 2, 2007. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108905.htm

2 Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA, MD. Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials. *JAMA*. 2007;297:1683-1696.

3 Wijlaars LPMM, Nazareth I, Whitaker HJ, et al. Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis. *BMJ Open* 2013;3:e003247. doi: 10.1136/bmjopen-2013-003247

4 Reeves RR, Ladner ME. Antidepressant-induced suicidality: An update. CNS Neurosci Ther 2010;16:227-234. Doi: 10.1111/j.1755-5949.2010.00160.x

In February 2016, the Food and Drug Administration (FDA) issued a clarification about safety issues related to Celexa (citalopram) dosing and warning recommendations.[5] Based on the possibility that high doses of citalopram can cause dangerous abnormalities in the electrical activity of the heart, the FDA made the following warnings and recommendations to providers:

- Citalopram causes dose-dependent QT interval prolongation, which can cause Torsades de Pointes, ventricular tachycardia, and sudden death.
- Citalopram is not recommended for use at **doses greater than 40 mg per day** because such doses cause too large an effect on the QT interval and confer no additional benefit.
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval.
- The maximum recommended dose of citalopram is **20 mg per day** for patients with hepatic impairment, **patients who are greater than 60 years of age**, patients who are CYP 2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet®) or another CYP2C19 inhibitor. These factors may lead to increased blood levels of citalopram and increase the risk of QT interval prolongation and Torsade de Pointes.
- Citalopram should be discontinued in patients found to have persistent QTc measurements greater than 500 ms.

Some antidepressants are FDA approved to treat pediatric patients diagnosed with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or childhood enuresis. The results of a survey conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) showed during 2007-2008 that 4.8 percent of adolescents (12 to 19 years old) took antidepressant medications.[6]

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5 U.S. Food and Drug Administration. Clarification of dosing and warning recommendations for Celexa. January 5, 2016. https://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm297764.htm

6 Gu, Q., Dillon, C. F., & Burt, V. L. (2010, September). Prescription Drug Use Continues to Increase: U. S. Prescription Drug Data for 2007–2008. NCHS Data Brief, No. 42. (DHHS Publication No. [PHS] 2010-1209). http://www.cdc.gov/nchs/data/databriefs/db42.pdf

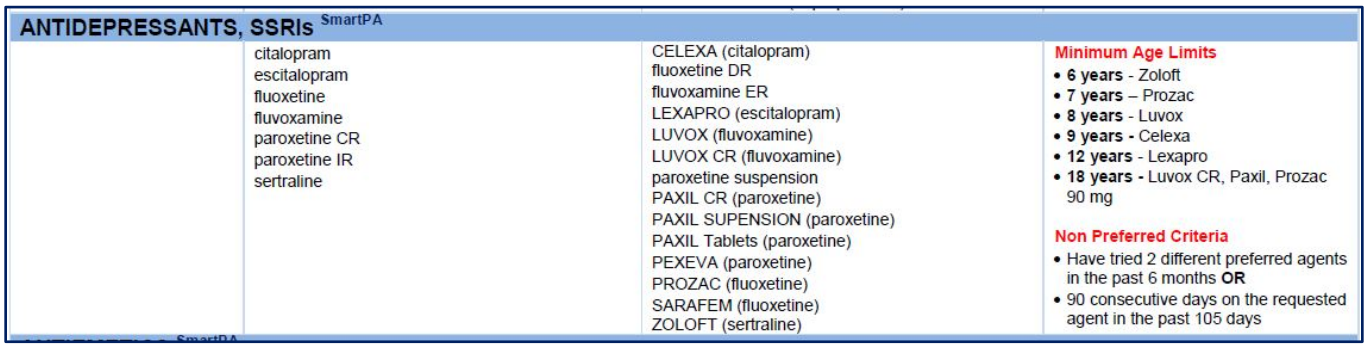
A fact sheet published by the Centers for Medicare and Medicaid (CMS) in 2013 provided guidance on the use of antidepressants in pediatric patients.[7] As shown in this table from the fact sheet, two of the tricyclic antidepressants (TCAs) – clomipramine and imipramine -- and only four of the selective serotonin reuptake inhibitors (SSRIs) -- escitalopram, fluoxetine, fluvoxamine, and sertraline -- have FDA-approved indications in pediatric patients.

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Antidepressant Medications

*Fluoxetine is FDA approved for the treatment of MDD in pediatric patients up to 18 years old.

According to the Celexa prescribing information, Celexa was studied in 407 pediatric patients in two placebo-controlled clinical trials. There was insufficient evidence to support a pediatric indication for the treatment of MDD.[8]

As shown in the Universal Preferred Drug List (UPDL) excerpt below, generic citalopram is a preferred product. In 2010, the Division of Medicaid (DOM) implemented an electronic prior authorization (PA) for SSRI antidepressants that included minimum age limits. The current age limit in the UPDL for citalopram is 9 years. All other age limits are consistent with the current FDA labeling for these products.



ANTIDEPRESSANTS, SSRIs SmartPA			
	citalopram escitalopram fluoxetine fluvoxamine paroxetine CR paroxetine IR sertraline	CELEXA (citalopram) fluoxetine DR fluvoxamine ER LEXAPRO (escitalopram) LUVOX (fluvoxamine) LUVOX CR (fluvoxamine) paroxetine suspension PAXIL CR (paroxetine) PAXIL SUPENSION (paroxetine) PAXIL Tablets (paroxetine) PEXEVA (paroxetine) PROZAC (fluoxetine) SARAFEM (fluoxetine) ZOLOFT (sertraline)	**Minimum Age Limits** • **6 years** - Zoloft • **7 years** – Prozac • **8 years** - Luvox • **9 years** - Celexa • **12 years** - Lexapro • **18 years** - Luvox CR, Paxil, Prozac 90 mg **Non Preferred Criteria** • Have tried 2 different preferred agents in the past 6 months **OR** • 90 consecutive days on the requested agent in the past 105 days

7 Centers for Medicare and Medicaid Service. Antidepressant Medications: Use in Pediatric Patients – Fact Sheet. https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ad-pediatric-factsheet11-14.pdf

8 Celexa® (citalopram) prescribing information. (2017, January 4). http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020822s047lbl.pdf

MS-DUR examined citalopram utilization to address the following research questions:

- How well is the current age edit working to restrict use in young children?
- What would be the potential impact of raising the age edit to 18?
- How often are the recommended maximum daily dose limits being exceeded?

METHODS

MS-DUR conducted a retrospective analysis using DOM's pharmacy claims for all programs (fee-for-service (FFS) and coordinated care organizations (CCOs)) for the period January 2016 – January 2017.

RESULTS

The **numbers of citalopram prescriptions claims** that DOM paid for each month are listed by the beneficiaries' ages in Table 1. Table 2 shows details on the number of prescriptions by month and beneficiary age for each pharmacy program. Overall utilization of citalopram has remained consistent during 2016 at approximately 3,000 fills per month while there was an increase of prescription claims during January 2017.

TABLE 1: Citalopram Prescription Claims by Month and Age of Beneficiary
(FFS and CCOs)

	Age at Fill					
Fill Month	**5 or less**	**6 - 8**	**9 - 17**	**18 - 59**	**60 +**	**Total**
2016- 1	1	5	425	2,335	282	3,048
2016- 2	0	6	401	2,286	277	2,970
2016- 3	1	5	442	2,380	311	3,139
2016- 4	0	2	392	2,121	273	2,788
2016- 5	1	5	403	2,239	296	2,944
2016- 6	2	1	401	2,244	305	2,953
2016- 7	2	4	364	2,170	279	2,819
2016- 8	0	3	456	2,259	280	2,998
2016- 9	0	4	445	2,149	293	2,891
2016-10	1	5	422	1,996	274	2,698
2016-11	1	3	419	1,929	289	2,641
2016-12	0	6	462	2,205	294	2,967
2017-01	1	6	504	2,899	405	3,815
Total	9	49	5,032	29,212	3,858	34,856

During 2016, 58 prescriptions for citalopram were filled for beneficiaries under the age of 9. The number of prescriptions claims for children under age 9 in the three pharmacy programs appeared to be proportional to the enrollment in each program. All three programs also had prescriptions filled for beneficiaries age 60 and over.

TABLE 2: Citalopram Prescription Claims by Month, Age and Pharmacy Program																		
	FFS						UHC						MAG					
Fill Month	Age at Fill						Age at Fill						Age at Fill					
	5 or less	6 - 8	9 - 17	18 - 59	60 +	Total	5 or less	6 - 8	9 - 17	18 - 59	60 +	Total	5 or less	6 - 8	9 - 17	18 - 59	60 +	Total
2016- 1	0	1	95	415	141	652	0	0	164	817	59	1,040	1	4	166	1,103	82	1,356
2016- 2	0	2	79	398	128	607	0	1	160	804	54	1,019	0	3	162	1,084	95	1,344
2016- 3	0	0	96	452	139	687	0	1	159	820	71	1,051	1	4	187	1,108	101	1,401
2016- 4	0	0	84	408	130	622	0	1	137	653	53	844	0	1	171	1,060	90	1,322
2016- 5	0	0	74	421	130	625	0	2	158	765	68	993	1	3	171	1,053	98	1,326
2016- 6	0	0	85	418	134	637	1	1	150	755	66	973	1	0	166	1,071	105	1,343
2016- 7	0	0	71	391	132	594	1	2	135	758	66	962	1	2	158	1,021	81	1,263
2016- 8	0	0	101	407	127	635	0	2	185	805	57	1,049	0	1	170	1,047	96	1,314
2016- 9	0	1	97	404	136	638	0	3	173	705	57	938	0	0	175	1,040	100	1,315
2016-10	0	3	86	377	125	591	0	2	162	674	49	887	1	0	174	945	100	1,220
2016-11	0	1	91	352	135	579	0	2	157	673	52	884	1	0	171	904	102	1,178
2016-12	0	3	85	367	124	579	0	2	195	907	69	1,173	0	1	182	931	101	1,215
2017-01	0	5	115	457	152	729	0	0	37	212	21	270	1	1	352	2,230	232	2,816
Total	0	11	1,044	5,267	1,733	7,446	2	19	1,935	9,348	742	11,813	7	19	2,053	14,597	1,383	15,597

Table 3 reports the **number of beneficiaries** by age and citalopram maximum total daily dose.

- Only 27 beneficiaries had maximum total daily doses that exceeded 40 mg/day. The majority of these beneficiaries were 18 to 59 years of age.
- 264 (39.5%) of beneficiaries age 60 or greater were prescribed greater than 20 mg/day.

TABLE 3: Maximum Daily Dose for Beneficiaries by Age
(FFS and CCOs - January 2016 - January 2017)

	Maximum Daily Dose*							
Age	**5mg**	**10mg**	**15mg**	**20mg**	**30mg**	**40mg**	**50mg +**	**Total**
5 or less	0	1	0	0	0	1	0	2
6 - 8	2	6	0	0	0	0	2	10
9 - 17	4	492	9	765	40	125	5	1,440
18 - 59	11	689	13	4,196	125	2,235	20	7,289
60 +	5	77	1	374	12	252	0	721
Total	22	1,265	23	5,335	177	2,613	27	9,462

** Daily dose calculated as (quantity dispensed / days supply * strength dispensed). Doses are rounded.*

Table 4 depicts the **number of prescriber**s writing prescriptions for targeted patient groups classified by age. Results were as follows:

- 30 different prescribers wrote prescriptions for children < 9 years of age.
- 26 different prescribers wrote prescriptions for daily doses exceeding 40 mg/day.
- 269 different prescribers wrote prescriptions for beneficiaries > 60 years old with daily doses exceeding 20 mg/day.

Overall, 314 different prescribers wrote prescriptions for one or more situations that were considered to be potential safety concerns.

TABLE 4: Number of Prescribers by Target Patient Groups
(FFS and CCOs - January 2016 - January 2017)

Children < Age 9		Adults Age 60+		Adults Age 60+ Prescribed > 20 mg/day		Beneficiaries Prescribed Daily Dose > 40 mg	
# Benes	**Number of Prescribers**	**# Benes**	**Number of Prescribers**	**# Benes**	**Number of Prescribers**	**# Benes**	**Number of Prescribers**
0	2,553	0	1,954	0	2,314	0	2,557
1	11	1	140	1	63	1	8
2	6	2	86	2	42	2	3
3	4	3	70	3	33	3	2
4	3	4	61	4	29	4	4
5+	6	5+	272	5+	102	5+	9

CONCLUSIONS AND RECOMMENDATIONS

The current age edit of 9 years appears to be effective with only a few prescriptions claims for children under age 9. Increasing the minimum age limit for citalopram to 18 years would have impacted 1,440 children and adolescent beneficiaries in 2016 (Table 3). However, fluoxetine, fluvoxamine, and sertraline which are preferred on the current universal PDL have pediatric indications for ≥ 9 years.

For adults, prescribing daily doses greater than 40 mg/day occurred infrequently and a hard edit for this population would have affected only 27 beneficiaries last year. Prescribing daily doses > than 20 mg/day for beneficiaries age ≥60 years would be somewhat more problematic. A hard edit for this daily dose would have affected 264 beneficiaries in 2016.

Recommendations:

1. DOM should implement an electronic PA edit to limit daily doses of citalopram to a maximum of 40 mg/day for beneficiaries less than age 60 years.
2. DOM should implement an electronic PA edit to limit daily doses of citalopram to a maximum of 20 mg/day for beneficiaries age ≥ 60 years.
3. DOM should raise the minimum age limit for citalopram in the SSRI electronic PA to 18 years to be consistent with the FDA approved citalopram label.
4. MS-DUR should conduct a one-time educational mailing reminding prescribers about age specific risks associated with citalopram and the FDA dosing recommendations. This mailing should include all prescribers writing citalopram prescriptions during the last year that were (a) for children and adolescents <18 years of age, (b) for adults age ≥ 60 years with daily doses > 20 mg, or (c) for adults age < 60 years with daily doses exceeding 40 mg.