

ANTIDEPRESSANT USE IN PEDIATRIC PATIENTS

Background

With the advent of fluoxetine (Prozac®) in 1988, a new era in the treatment of depression began. Since fluoxetine, several therapeutically similar agents have been approved constituting a group of drugs commonly referred to as ‘newer generation’ antidepressants. These drugs, including selective serotonin reuptake inhibitors (SSRIs) and some chemically unrelated agents (bupropion, venlafaxine, and mirtazapine) have largely replaced older pharmacologic treatment modalities in the management of major depressive disorders in both adults and children due to equivalent or superior efficacy to older agents and an improved side-effect profile.¹

Despite abundant safety data collected over the years for these drugs, an important issue first recognized in 1990 returned again to the forefront of media attention and clinical debate in March 2003: an alleged increased risk of suicide, especially in pediatric patients.^{2,3} The British Department of Health was the first to act, warning prescribers in the UK to avoid the off-label use of SSRIs in patients under the age of 18. The FDA issued similar warnings and a “Dear Doctor” letter to prescribers in the US. As pressure mounted from individuals and public advocacy groups, the FDA conducted an in depth investigation which culminated in a “black box” warning being added to the product labeling of several commonly used antidepressants (see table below) encouraging prescribers to closely monitor the behavior of pediatric patients following antidepressant initiation or dose changes. In addition, a Medication Guide describing the risks of antidepressants in pediatric patients and monitoring recommendations is to be provided with all new and refill prescriptions.⁴

Comparison of “Newer Antidepressants”

Generic Name	Brand Name(s)	Typical Adult Dose	Cost*		Approved for Pediatric Patients?	
			Brand	Generic	MDD	OCD
Bupropion	Wellbutrin	100mg TID	\$133.20	\$110.97	No	No
	Wellbutrin SR	150mg BID	\$123.97	\$94.59		
	Wellbutrin XL	300mg QAM	\$116.18	N/A		
Citalopram	Celexa	20mg QD	\$74.99	N/A	No	No
Escitalopram	Lexapro	10mg QD	\$66.60	N/A	No	No
Fluoxetine	Prozac	20mg QD	\$114.40	\$25.99	Yes	Yes
	Prozac Weekly	90mg Q week	\$90.88	N/A	No	No
Fluvoxamine	Luvox	100mg BID	N/A	\$87.69	No	Yes
Mirtazapine	Remeron	30mg QHS	\$107.97	\$46.69	No	No
	Remeron SolTab	30mg QHS	\$95.97	\$87.97		
Nefazodone	Serzone	200mg BID	N/A	\$39.69	No	No
Paroxetine	Paxil	20mg QD	\$87.48	\$73.39	No	No
	Paxil CR	25mg QAM	\$87.54	N/A	No	No
Sertraline	Zoloft	100mg QD	\$82.50	N/A	No	Yes
Venlafaxine	Effexor	75mg BID	\$113.40	N/A	No	No
	Effexor XR	150mg QD	\$102.26	N/A		

*Cost based on AWP for 30 day supply (at typical dosage) per 2004 Redbook
MDD=Major depressive disorder OCD=Obsessive compulsive disorder

Suicide Risk

The case series published in 1990 first identifying a possible link between SSRIs and an increased risk of suicide described six patients who became intensely suicidal shortly after initiation of fluoxetine.² Successive reports involving other SSRIs led authors to postulate that this may be a class effect with serotonergic antidepressants.⁵ Although there are several theories to explain this alleged increase in suicidal behavior, three main hypotheses are the current focus. First, it has been suggested that the activating potential of serotonergic drugs, often apparent early in treatment, may give depressed patients sufficient energy and drive to successfully complete a suicide attempt before cognitive benefits are realized, which often takes much longer (4-6 weeks). A second hypothesis suggests that akathisia, a rare adverse effect of these agents (occurring in <5% of patients) is to blame. Akathisia is manifested as agitation and hostility and may also trigger suicidality. Third, it has been theorized that use of one of these agents in a patient with undiagnosed bipolar disorder may result in mood destabilization and an increased risk of suicide. Despite these theories, antidepressant-induced suicidality is still poorly understood. Much of the uncertainty can be attributed to the inherent difficulty of demonstrating causality in a population clearly inclined toward suicide.³

Evidence from the literature

Although epidemiologic studies point to a dramatic increase in antidepressant use over the past decade, the rate of successful suicides has declined. In addition, randomized clinical trial data from over 20,000 depressed adults taking SSRIs has revealed no convincing evidence that this class increases suicide risk compared with placebo.³ The evidence available for antidepressants in pediatric patients consists of short-term (4 to 16 weeks) placebo-controlled trials involving over 4,400 patients with MDD, OCD, and other disorders. The average risk of suicidality in these trials was 4% (twice the placebo risk), although no suicides actually occurred in these trials.⁶

Conclusion

Although the preponderance of evidence suggests that antidepressants do not increase suicidality in adults, evidence from pediatric trials points to a small, but statistically significant increased risk. The FDA recommends increased monitoring of pediatric patients, especially upon initiation of one of these agents and with dosage changes (increase or decrease). Ideally, weekly face-to-face contact with patients and/or family members is advised for the first 4 weeks, biweekly visits for the next 4 weeks, another visit at 12 weeks, and as clinically indicated thereafter. Despite these recommendations and current media attention, it is also important to emphasize to patients that based on current information, untreated depression carries a far greater risk of suicide than does any antidepressant medication.

References

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