

Anti-depressants: *Controversies, Challenges, and Solutions*

CMHDA Medical Services System of Care Committee

The use of antidepressant selective serotonin reuptake inhibitors (SSRI's) , other newer antidepressants, and their link to suicidality (suicidal thoughts and/or behavior) and suicide (actual death) has been an intense area of controversy at both the federal and state levels during the past year. Congress and the Federal Drug Administration (FDA) have each held numerous contentious hearings during 2004. In California during August 2004, Senator Tom Torlakson (as Chair of the CA Task Force on Youth and Workplace Wellness) and Senator Deborah Ortiz (as Chair of the Senate Health and Human Services Committee) convened a Joint Informational Hearing, "Antidepressants and Suicide". Senator Torlakson clearly has a strong interest in ensuring the safety of individuals -- especially children -- who take SSRI's; his adult niece died from suicide, and apparently was on an SSRI at the time of her death. During the hearing he proposed that all physicians have each one of their patients for whom SSRI's are prescribed sign an informed consent form that indicated that suicide was a complication of taking SSRI's. He has publicly acknowledged that the informed consent practice in the public mental health sector should be replicated in the private sector. Senator Torlakson introduced SB 524 in February 2005 which, if passed, would mandate that all physicians receive extra education on the treatment of depression and that the California Medical Board monitor this mandate.

Evidence-Based Treatments of Depression

Depression is indeed a serious illness, in both adults and children. 7.1% of Americans ages 18-54 have Major Depressive Disorder or another serious mood disorder. The National Institute for Mental Health (NIMH) estimates that in any year, 19 million Americans over the age of 18 suffer from depression. The human and financial tolls are immense. In 2001, 30,622 Americans committed suicide. The estimated financial costs of depression approach \$50 billion annually.

Depression can strike at any age. At any given time, as many as 2.5% of children and 8.3% of adolescents in the U.S. have depression. In fact, suicide is the third leading cause of death in adolescents. Approximately 2,000 children and adolescents die of completed suicide each year, although this number has steadily decreased in recent years. According to a recent study, a 1% increase in prescription in antidepressant medication has been associated with a 0.23 decrease in suicide per 100,000 in adolescent suicides. Each year approximately 17% of all adolescents report suicidal thinking, according to the Centers for Disease Control and Prevention. Depression is one of the most treatable psychiatric or medical illnesses, with 80-90% positive responses to treatment. Yet, unfortunately, as many as 47% of children with mental illness do not receive care. Childhood access to treatment for depression is already limited, and this fact is of major concern, not only because of the associated morbidity and death risk associated with active depression in children, but also because untreated depression in childhood may lead to long-term depression and psychosocial impairment in adulthood.

There is overwhelming scientific evidence that antidepressants are effective in adults. Similar evidence exists for fluoxetine (Prozac) in children and adolescents. Nevertheless, other newer antidepressants are used with children and adolescents in "off-label" fashion. "Off-label" practice refers to the use of any medication for which there are no studies of safety and efficacy that have been reviewed by the FDA; this is also referred to as FDA non-approval. Off-label

usage in children and adolescents is important because only about 30-40% of children and adolescents will respond to an initial antidepressant. Off-label practice in the general medical community suggests that other newer antidepressants are used effectively after other treatment efforts, including talk therapies, have been exhausted and/or there is significant clinical deterioration. In addition to medication, studies of depression treatment show that behavioral therapies, especially cognitive-behavioral therapy (CBT), work to treat depression. A very recent study sponsored by the National Institute of Mental Health concluded that fluoxetine in combination with CBT led to significant improvement in 71% of moderately to severely depressed youth. When therapy is used without antidepressant medication, it is not as effective as medication. On the other hand, a combination of antidepressant medication plus therapy is more effective than either, alone. There is further evidence that family therapy, especially in children and adolescents, may be an important adjunctive intervention with antidepressant medication. Talk therapies are known to decrease suicidality among children and adolescents.

A recent Swedish study demonstrated no association between suicide and some commonly prescribed selective serotonin reuptake inhibitors ("SSRI's") used for depression. Forensic toxicology screens of 14,857 suicides were compared with 26,422 natural or accidental deaths between 1992 and 2000. The researchers were able to demonstrate a significantly diminished association with suicide with 3 different SSRI's.

Federal Drug Administration Issues

The FDA has implemented the following "Black Box Warning" in February 2005 (*in italics*):

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use)

Note that the FDA did not state that the use of antidepressants is causally linked to suicide or suicidality. There is an increased risk for suicidality (thinking and behavior suggesting a desire to die) only, not suicide. Increased risk of suicidality is not the same as causing suicidality. It is also important to remember that there are many other risk factors for suicidality in young people.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drugs was 4%, twice the placebo risk of 2%. No suicides occurred (among children and adolescents) in these trials.

The FDA has also instituted new practice recommendations (*in italics*), published as part of a warning letter to parents and caretakers, as follows:

After starting an antidepressant, your child should generally see his or her healthcare provider:

- *Once a week for the first 4 weeks*
- *Every 2 weeks for the next 4 weeks*

- *After taking the anti-depressant for 12 weeks*
- *More often if problems or questions arise*

These recommendations are obviously not feasible in the public mental health sector, as discussed in a subsequent section.

Controversy Related to the FDA position

Antidepressant medications are generally used as the cornerstone in the treatment of major depression, as evidence suggests that they are the most singularly effective treatment available, alone or in combination with other psychosocial modalities in adults. Some recent evidence suggests that CBT is as effective a treatment as antidepressants. Evidence supporting the use of antidepressants is less robust in children with the exception of Prozac, only one of several newer anti-depressants. However, the FDA has imposed new medication warnings and practice standards for the prescription of antidepressants, particularly applicable to children. The net effect of these actions may be to limit further the already limited access that children have, to effective care for their illness.

The actions of the FDA are based on limited data, and may be ill-advised. A key problem is that the FDA has generally not required testing of antidepressants in children, so research trials were designed for children only in limited situations where pharmaceutical companies wished to extend patent lives. The overwhelming body of information regarding use of these medications in children has been accumulated by clinicians in practice, using the medications in an "off-label" fashion, a practice common in both primary and specialty medical fields. The FDA's limited review of studies has noted an increased risk of suicidality (thoughts and behavior) of 4% in antidepressant treated youngsters versus 2% for children on placebo, but NOT as an increased risk of suicide. It must be noted that the risk of increased suicidality, e.g. suicidal thinking or preoccupation, has not been definitively linked to completed suicide in research data for either children or adults.

In fact, our society has witnessed a diminished rate of suicide in children and adolescents since the time that Prozac was placed on the market. (However, there is no study that concludes that this decrease in suicide is causally linked to the introduction of SSRI's on the market). It is well known that suicidality is strongly linked to severe depression. There is simply insufficient evidence to suggest that antidepressant treatment is linked with increased risk of suicide. *Furthermore, there is also a strong belief among community psychiatrists that undue warnings and restrictions on practice will inevitably lead to diminished access for children, which will likely create the far greater risk of suicide due to untreated severe depression.*

Positive Aspects of FDA Position

An increased awareness of the risk for suicide in depressed patients may result, where resources are available, in closer monitoring of those who receive antidepressants. There is clear evidence that the addition of psychosocial interventions to medication treatment, including behavioral and family therapies, improves treatment outcomes. Patients and families could benefit from more psycho-education. It is hoped that the FDA warnings may stimulate third party payers, like HMO's, to cover more medically necessary non-pharmacological intervention strategies, in addition to medication visits.

Negative Aspects of FDA Position

It has already been noted that access to services is a problem, especially for children. There is a severe shortage of psychiatrists, especially child psychiatrists, both nationally and in California, as

reported by the California Mental Health Planning Council. This is equally true in the public and private sectors. The new FDA practice requirements will spread current psychiatric providers thinner, occupying more of their time, and diminishing their availability for additional evaluations and patient care.

The FDA warnings will "scare away" both childrens' parents and caretakers; anecdotal evidence supports this trend. Unnecessary fear of medication, promoted in the FDA publications, is written in "black and white." The greater concern should be that of suicidality in the untreated child, but, since that fear is more speculative, the FDA's warnings will convince many well-meaning parents to avoid definitive antidepressant treatment. While the research has not causally linked SSRI usage with suicide, clearly more untreated depression may likely result in higher suicide rates among children.

Access will be additionally strained by the fear of primary care providers, especially family practitioners and pediatricians, who have increasingly prescribed antidepressants appropriately to children over the last years and, in the public sector, have shared the burden of treating children and families. At least one major health plan in the east coast has reported that the number of prescriptions for SSRIs has significantly diminished during the period of controversy dating back to at least last year. Primary care doctors traditionally have not had the time or infrastructure to assure the close medication supervision that the FDA now recommends. The Wall Street Journal carried an article in Fall 2004, already documenting the fact that even affluent families across the country were finding themselves incapable of obtaining antidepressant treatment for their depressed children. The problem arose due to the new refusal of primary care providers to prescribe, coupled with the fact that local child psychiatrists already had long waiting lists for new patients.

Workforce and Treatment Team Issues

Many counties will simply be unable to meet the new FDA practice recommendations, due to the shortage of child and adolescent psychiatrists. Many rural counties are especially resource-poor, and the additional time that psychiatrists now will spend in personally monitoring patients on newly prescribed antidepressants will further limit access for new patients. In addition, the anticipated diversion of depressed patients from both the private and primary care systems will further decrease access to psychiatrists in the public sector. Already strained counties will need to compete for additional psychiatrists at a time of acute shortage. This may result in an increase in the usage of care in acute settings, including public psychiatric beds.

The new FDA practice recommendations assume that the prescribing physician should provide the follow-up monitoring after an antidepressant is prescribed. In California, however, the Rehabilitation Option (of Medicaid) provides for an interdisciplinary team approach. Others within the team, besides the prescribing physician, may be much more familiar with the client than the doctor. Nurses, clinicians, and paraprofessional case management staff often have a much closer, ongoing relationship with the client and the client's family or other support system. A premise of the Rehabilitation Option is that the client deserves to benefit from contact with the individual provider on the team who is best able to engage with the client. Thus, in the Rehabilitation Option, non-medical providers of the treatment team, who work closely with a prescribing physician, are often in the best position to provide close patient monitoring after antidepressants are prescribed. Furthermore, the American Academy of Child and Adolescent Psychiatry suggests strategies for parents to help monitor medication response including suicidality; this practice underscores a system of care principle in which parents are valued partners in the system of care.

Informed Consent

In an interdisciplinary Rehabilitation Option context, informed consent for medication is part of an overall process of team engagement and psycho-education for the client and the client's support system. Informed consent is not a single episode of exchange of written documentation; rather, it is an ongoing process that is a facet of treatment partnership. In the case of children and adolescents, the young client must be given an explanation commensurate with their developmental level. Therefore, as an alternative to the FDA practice requirements, California counties have the opportunity to engage patients and families in an ongoing process of informed consent that provides for a continuous exchange of information about a patient's status. In many respects, this engagement may provide for safer patient monitoring, not only just after antidepressants are started, but also on an ongoing basis.

New Opportunities

Implementation of best practices is particularly limited by workforce limitations. There has been a serious shortage of psychiatrists. The FDA's new position may be a wake-up call, which can serve to remind us that the further attenuation of psychiatric services may be dangerous to client safety. Clearly, more psychiatrists must be trained, to address the needs of our communities. The Mental Health Services Act may provide an opportunity to work with universities to develop additional residency training slots, specifically for community psychiatry.

In addition, a more immediate response may be required in many of our counties, where a sustained psychiatrist shortage will be a reality for some time. Further training of non-physician behavioral specialists would allow them to do a better job assisting in the monitoring of patients on medications. Ideally, every member of the interdisciplinary team could be capable of participating in the psycho-education that patients and families need in order to better understand their illnesses and treatment options.

Lastly, greater collaboration between mental health and primary care will ultimately be crucial to increasing access to psychotropic treatment, since many clients – especially in some minority communities – much prefer treatment in the primary care setting. Extension of county mental health services to support primary care doctors with consultation and liaison services can be a cost effective way to assure that the greatest number of citizens will have access to quality care for mental illness.

Recommendations:

- 1) Written informed consent should be documented in the medical record, and there should be a continuing quality improvement mechanism to monitor compliance with this requirement.
- 2) The physician and others on the treatment team should provide psycho-education about depression, treatment alternatives, the prescribed medication and the relevant side effects.
- 3) Patients and their supports should have ready access to a crisis worker or other mental health provider at all times, in case questions or problems arise.
- 4) Families and other supports, wherever accessible to the treatment team, should be included in information regarding the patient's need for monitoring.
- 5) Monitoring should take into account developmental considerations, so that care is adapted to the varying needs of children, adolescents, adults, and older adults.
- 6) Assignment of staff for actual patient visits for follow-up monitoring, in a multidisciplinary system, should reflect individualized clinical judgment based on the

skills of the different team members, the degree of valuable client engagement each might have, and the patient's preference.

- 7) While the specific FDA practice language may be used as a recommendation, the specific frequency of monitoring visits should be individualized, and based on the specific client's needs. In some cases, a patient may need more frequent visits. In other cases, where there is an exceptionally strong and knowledgeable support system, less frequent visits may be needed.
- 8) Phone contacts may be used for patient monitoring, when there is an established, positive working alliance with a patient and their family or other supports.
- 9) Within the limits of each county's resources, a comprehensive treatment plan for a patient with depression should incorporate evidence-based, non-pharmacological treatment interventions as well as medication, to provide optimal treatment response.

ADDITIONAL INFORMATION

A physicians' medication guide and a parents' medication guide at www.parentsmedguide.org

Federal Drug Administration on antidepressants at
www.fda.gov/cder/drug/antidepressants/default.htm