The Journal of Mind-Body Regulation

commentary

What Are Pediatric Antidepressant Meta-Analyses Telling Clinical Practitioners? It Depends…

Commentary: ***A Meta-Analysis of Randomized Placebo Controlled Trials of Antidepressant Medications in Depressed Children: Do the Benefits Justify the Risks?***

Julie M. Zito, PhD*

June, 2011

Drews, Antonuccio and Kirsch present a compelling case for questionable effectiveness based on a meta-analysis of 19 randomized, double blind clinical trials among children and adolescents to evaluate antidepressant (ATD) efficacy in several ATD subclasses, i.e. SSRI, SNRI and TCAs. The analysis expressed the summary effect size 'd' for drug-treated vs. placebo-treated groups, after computing the effect size (primary endpoint minus baseline score divided by the pooled standard deviation). The total 'd' was 1.62 for drug and 1.36 for placebo among all 19 studies for a between-group difference of 0.26, thus showing that 84% of drug effect is duplicated by placebo response. One might quibble about the value of adding so many old TCA studies which were well documented by 1999 to lack evidence of benefit (Geller et al., 1999). However, when the TCA studies were excluded, the 11 SSRI and SNRI studies showed placebo duplicated 86% of the active drug response although the between group difference is ten-fold greater than when the TCAs were included. Still, whether in all trials or only SSRI/SNRI trials the overall group benefit is slight, and statistical significance does not equate with clinical significance.

If one further argues that clinical trial patients are more ideal than the community population that will be treated with an ATD, one's skepticism of benefit grows because the trials favor more cooperative patients who may have had greater family expectation of a positive drug effect, and may have achieved a level of benefit from the *structure of the trial itself*, i.e. providing regular contact with caring staff whose attention and championing support to complete the study may have added non-pharmacologic benefit. Given the high placebo response in these youth, the net "trial effect" across all subjects might further contribute to the close response in the two groups.

In addition, one influential analysis showed that age-stratified benefit in children less than 12 years of age only favored fluoxetine and concluded that SSRI benefits for MDD were moderated by age group, duration of depression and study conditions (Bridge et al., 2007).

ATD safety concerns emerged in 2003–4 and contribute to the importance of demonstrating reliable ATD benefits in order to avoid unnecessary risk, as well as unnecessary monetary costs, a critically important point in tight economic times and runaway drug costs for brand name products. The meta-analysis published by FDA investigators found that the safety signal based on suicidality (thoughts, attempts or completions) was significantly greater for drug-treated compared with placebo-treated youth, albeit rare (4% vs 2%) and with no completed suicides (Hammad et al., 2006). A noted clinical trialist in ATDs has criticized the safety analysis in terms of the metric of using suicidal ideation as a surrogate for suicide because there is no measurable correlation between

* *Professor of Pharmacy and Psychiatry, University of Maryland, Baltimore*

email: jzito@rx.umaryland.edu

suicidal thoughts and attempts or completions (Klein, 2006). An additional concern is the extensive broadening of the warning to all ATDs although only SSRIs and SNRIs had data showing a concern. Later warnings extended to those less than 24 years old and to antiepileptic drugs, whether used as mood stabilizers or not. These later decisions, in the face of skepticism that the original metrics were worthy of such interpretations, probably demonstrates the 'cry wolf' syndrome—if all ATDs are equally risky, we might dismiss the risk issue completely. Labeling all ATD subclasses should not dismiss the uncertainty of safety for SSRIs and SNRIs. Rather it should be interpreted as a call to action for (prospective) active surveillance of a large well-diagnosed youth cohort, primarily adolescents, with well-described prior histories that stratify by severity of illness, in order to better address the risk question in conjunction with data on benefit, length of exposure, dosing information, outcomes and reasons for discontinuation.

Several additional critical factors might be considered in relation to a physician's decision to use an ATD to treat pediatric depression. Among the factors I suggest should be included are: 1) Physician awareness of the controversies surrounding antidepressant efficacy since their early development in the 1960s. 2) Drug safety from post-marketing surveillance and from clinical trial meta-analysis of adverse drug event risk; 3) The general acceptance of biological psychiatry as a theory of psychiatric/behavioral abnormalities in a wide range of arenas. These include research leaders, the lay public, and the media in conjunction with marketing and research in support of a biological theory, which persists despite inadequate evidence or flawed interpretation. 4) The growth of comorbid diagnoses in the evolving Diagnostic and Statistical Manual (DSM) and the distinctly differing professional perspectives depending on one's primary discipline (Beutler & Malk, 2002). 5) The distinct role of the prescribing doctor now being limited to 15 minute 'med check' evaluations in contrast to the clinical psychologist's role of psychotherapist and referral for drug therapy. Added to this issue is the great variation in treatment settings and reimbursement systems. These topics are briefly discussed in the context of this meta-analysis to assess benefit of pediatric antidepressant use over placebo in children and adolescents for the treatment of depression.

The antidepressant efficacy challenge

In 1985, Baldessarini's review of TCAs for the treatment of adult depression concluded that trial support of a drug benefit was largely restricted to severe (usually hospitalized) depression (Baldessarini, 1985). The challenges for lesser depressions include spontaneous remission, response to psychotherapy and non-specific treatments e.g. placebo and anxiolytics. Thus, clinicians can mistakenly view the temporal association of drug use and improvement as *causal*. These design issues are still true today for the newer subclasses of serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), and may be more so in youth, particularly young children. In summary, the high pediatric placebo response along with relatively greater adverse events such as hostility and agitation/activation, and greater dropout rates, make recommendations for ATD use in children for major depression questionable.

Additional challenges reside in the limitations of clinical trial methodology, the so-called gold standard in medical care, with respect to selection bias; reductionist measures of diagnosis which rely more on current symptoms than on past history and the degree of impairment; design modifications to strengthen positive results (Safer, 2002); and publication bias. Investigators have questioned the merits of analyzing the published trials when publication bias in pharmacologic research is common and the estimates of efficacy may essentially reside in the published studies (Whittington et al., 2004).

In the studies of efficacy in youth, there are important age-related distinctions in efficacy of the SSRIs that are glossed over in the ensuing debate. Safer's secondary analysis

of published studies shows efficacy for adolescents but not for children (Safer, 2006). A similar finding for TCA efficacy was demonstrated previously and concluded that TCAs are modestly effective in treating depression in adolescents, with concerns about side effects and safety further limiting their use (Hazell et al., 2002).

Drug safety concerns

In general, the safety of pharmacologic agents is best studied after marketing because short-term use in drug trial populations does not generalize to long-term use in community-treated populations (Zito and Safer, 2007). The limitations of the existing infrastructure for monitoring drug safety have been noted (Klein, 2006), not least of which is the absence of denominator data which makes systematic assessment of the risk (incident data) impossible. These concerns have led to louder calls for active surveillance systems and the FDA's sentinel initiative is, in part, an effort to improve assessment of the risk of adverse drug events after marketing (Psaty and Charo, 2007).

Biological psychiatry as a theory of mental illness

The rise of biological psychiatry as a theory of mental illness since the 1980s has been extraordinary. It can be argued that a chicken and egg model confounds our understanding. Which came first, the drug mechanism of action affecting neurotransmitters or the newly define disease etiology? There is little doubt that medications have played an important role in reducing the suffering of those with severe conditions, e.g. schizophrenia, bipolar disorder and in developmentally disabled children with self-injurious behaviors. However, the mechanism of action of a drug, while necessarily connected to symptom control and possibly reduced impairment, is not sufficient to explain the *cause* of these problems. Neurotransmitters are changed by drugs, e.g. increasing serotonin at the synapse in depressives. However, this change in brain chemistry does not make depression a serotonin deficiency condition. Nor is bipolar disorder a lithium-deficiency disorder. Yet, these simplistic notions are exactly how the media and many patients and their families have come to understand psychopharmacology. If unaddressed, there is a risk that such reductionist scientific thinking will lead to scientism rather than to critically important scientific evidence.

The DSM-ification of child mental health

As the DSM classification system for mental illness is evolving, a major change is seen in the increase in comorbid conditions (Pincus et al., 2004). This may be occurring because of an emphasis on the presence of symptoms derived from checklists and diminished emphasis on impairment. Whatever accounts for this change in comorbidities, the result in terms of medication treatments is clear—more comorbidities tends to produce more concomitant medication use. More medication use increases the risk of adverse events, although clinicians may believe that 2 drugs at lower doses reduce the risk of adverse events from either alone at a higher dose. There is no evidence to support this belief, although there are empirical studies supporting the notion that drug combinations increase the prevalence of adverse events (Turner et al., 1998).

Population, treatment setting and reimbursement systems

Across western society, there are radically different reimbursement systems which may affect the ability of a clinician to judge a drug-related outcome. This is particularly acute in the US health care system where patterns of continuity of care are not well known. Its impact in pediatrics can be significant (Christakis et al., 2002). For internalizing emotional health conditions, such as depression and anxiety, the failure to monitor symptom control and reduced impairment in subsequent time periods is troubling because new treatment-emergent symptoms may not be recognized as behavioral toxicity and mistakenly attributed to new symptoms of underlying pathology (Zito et al., 2008). In addition, when

patients move from provider to provider it is nearly impossible to avoid adding additional drugs in order to resolve what appear to be illness- related rather than drug-related (treatment-emergent) symptoms. Systems based on primary catchment areas, as in the UK, maximize continuity of care and afford the best possible chance to gain experience in long-term effectiveness and safety of psychopharmacologic agents.

In the final analysis, the benefits and risks of drug treatment in community-based children and adolescents with mental disorders should be viewed as a constantly moving target, once the FDA approval for marketing occurs. As data and experience grow, the benefit–risk assessment is subject to change. Moreover, prescribing physicians and their patients each carry their own personal perspective on benefit/risk derived from various pre and post marketing data, and the subsequent slowly emerging drug safety reports from studies would help to identify the small but important subset of patients who cannot tolerate SSRIs. This distinction is key in the decision to use drug therapy or to engage in non-drug alternatives including, when possible, watchful waiting. The experience of regular return visits would offer the opportunity for spontaneous remission or resolution of the precipitating symptoms to be recognized by the treating physician and help to make post-marketing surveillance of effectiveness and safety a reality.

The meta-analysis of *grouped* ATD benefits in children and adolescents presented by Drew, Antonuccio, and Kirsch helps clinicians to appreciate that decisions to treat depression with an ATD relate to age, severity and prior history in their patients and calls for continuity of care and monitoring so that benefits and risks in the *individual* can be observed. Large prospective cohort studies would help to identify the small but important subset of patients who cannot tolerate SSRIs.

References

Drews, A. A., Antonuccio, D. O., Kirsch, I. (2011). A meta-analysis of randomized placebo controlled trials of antidepressant medications in depressed children: Do the benefits justify the risks? *The Journal of Mind–Body Regulation, 1*(2), 85–95.

Baldessarini, R. J. (1985). Antidepressants. In R. J. Baldessarini (Ed.), *Chemotherapy in Psychiatry: Principles and Practice*. Cambridge: Harvard University Press.

Beutler, L. E. & Malk, M. A. (Eds). (2002). *Rethinking the DSM: A Psychological Perspective*. Washington, DC: APA.

Bridge, J. A., Iyengar, S., Salary, C. B., Barbe, R. P., Birmaher, B., Pincus, H. A., . . . Brent, D. A. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association, 297*, 1683.

Christakis, D. A., Wright, J. A., Zimmerman, F. J., Bassett, A. L., Connell, F. A. (2002). Continuity of care is associated with high-quality care by parental report. *Pediatrics, 109*, e54.

Geller, B. G., Reising, D., Leonard, H. L., Riddle, M. A., Walsh, B. T. (1999). Critical review of tricyclic antidepressant use in children and adolescents. *Journal of the American Academy of Child Adolescent Psychiatry, 38*, 513–516.

Hammad, T. A., Laughren, T., Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry, 63*, 332–339.

Hazell, P., O'Connell, D., Healthcote, D., Henry, D. A. (2002). Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews, 2*, CD002317.

Klein, D. F. (2006). The flawed basis for FDA post-marketing safety decisions: The example of antidepressants and children. *Neuropsychopharmacology, 31*, 689–699.

Pincus, H. A., Tew, J. D., First, M. B. (2004). Psychiatric comorbidity: Is more less? *World Psychiatry, 3*, 18–23.

Psaty, B. M., Charo, R. A. (2007). FDA responds to Institute of Medicine drug safety recommendations-in part. *Journal of the American Medical Association, 297*, 1917–1920.

Safer, D. J. (2002). Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *The Journal of Nervous and Mental Disease*, *190*, 583–596.

Safer, D. J. (2006). Should selective serotonin reuptake inhibitors be prescribed for children with major depressive and anxiety disorders? *Pediatrics, 118*, 1248–1251.

Turner, S., Longworth, A., Nunn, A. J., Choonara, I. (1998). Unlicensed and off label drug use in paediatric wards: prospective study. *British Medical Journal, 316*, 343–345.

Whittington, C. J., Kendall, T., Fonagy, P., Cottrell, D., Cotgrove, A., Boddington, E. (2004). Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet, 363*, 1341–1345.

Zito, J. M., Safer, D. J. (2007). The efficacy and safety of selective serotonin reuptake inhibitors for the treatment of depression in children and adolescents. In R. Mann & E. B. Andrews (Eds.), *Pharmacovigilance* (pp 559–570). New York, NY: John Wiley & Sons.

Zito, J. M., Safer, D. J., Craig, T. J. (2008). Pharmacoepidemiology of psychiatric disorders. In A. G. Hartzema, H. H. Tilson, K. A. Chan, (Eds.), *Pharmacoepidemiology and Therapeutic Risk Management* (pp 817–854). Cincinnati, OH: Harvey Whitney Books.