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Applying Bioethics to Pediatric Psychopharmacology

A Guide for Clinicians with Case Studies and Handouts

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Introduction
Perhaps no area of child psychiatry is as fraught with ethical complexity as psychopharmacology. On the one hand, there is an increased demand for child psychiatric assessment and treatment. On the other, the evidence base for medication treatments in community populations is often uncertain. While there are multiple social, cultural and institutional issues that influence our medical behavior, the ultimate responsibility rests with the prescribing psychiatrist.

The first goal of this paper is to give clinicians a theoretically sound approach to complex medical decisions, with discussion using typical cases. The Four-Topics Method alluded to in the main text, organizes the Basic Principles (respect for dignity, non-maleficence, beneficence, justice) into four decision-points: 1) Medical indications, including history, diagnosis, prognosis; 2) Patient preference; 3) Quality of life; and 4) Contextual features. (Jonsen et al, 2006). To this framework is added ethicist Thomas Murray’s concept of mutualism. This principle, which delineates parental responsibility in medical decision-making, states the following: Parents have a unique moral duty to create enduring, caring relationships with their children. Caring for children’s unique needs also promotes parental flourishing. We cannot choose our children, any more than they can choose us. Ethics furthermore instructs doctors to promote institutions that facilitate mutualism.

A second, related goal is to help the clinician navigate the evidence. Numerous reviews have pointed to flaws in commonly accepted practice, both in medicine generally, and specifically in pediatric psychopharmacology. These include: introduction of bias in pharmaceutically sponsored clinical trials and institutional protocols, withholding of data by pharmaceutical companies, ghost-writing of academic articles, direct payment to physicians to prescribe medications, and clinical trial design that were of inadequate duration to detect some adverse outcomes, or did not generalize well to community populations. (Albert, 2004; Als-Nielsen et al, 2003; Berenson, 2006; Brennan et al, 2006; Campbell et al., 2006; DeAngelis and Fontanarosa, 2008; Landerfield and Steinmen, 2009; Morin et al., 2002; Rothman et al., 2009; Sexton, 2006, Zito et al., 2008a,b; Rothman et al., 2009). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and Evidence Based Medicine (EBM) Working Groups have written a series of papers that detail steps which can help physicians critically examine scholarly articles in the service of developing evidence-based practices (Guyatt et al., 2000, 2008 a and b, 2011 ).

Addendum 1 synthesizes the Four Topics Method (Jonsen et al., 2006) and Mutualism (Murray, 1996) for pediatric psychopharmacology.

Addendum 2 lists some key points from the GRADE articles and the Cochrane Handbook, to help child psychiatrists read studies with a critical eye.

Epidemiology of Pediatric Psychopharmacology
The use of medications for children’s emotional and behavioral disorders has risen dramatically since the 1980’s with evidence often lagging use (Zito et al, 2000). The use of antidepressants for depressive syndromes (as opposed to major depressive disorder [MDD]) has decreased since the FDA’s black box warning of 2004 (Zito, 2011); however, the use of antipsychotics in non-psychotic children continues to escalate, even in very young children (Olfson et al, 2010; Comer et al, 2010; Eggers 2010; Zito 2008a). Emerging data indicate that atypical antipsychotics and SSRI’s can have significant adverse effects on metabolism (including bone growth), cardiovascular status and increased risk of diabetes as well as dykinesias (Correll and Carlson, 2006; Bliziotes, 2010; Jerrrell, 2009; McIntyre and Jerrell, 2008, Fountoulakis et al., 2006, Hammerman et al., 2006; Wonodi et al., 2007, Hollis and Thompson, 2007).

Studies of prescribing patterns suggest that psychotropics, and in particular the atypical antipsychotics (AAP’s) are being used for heterogeneous symptoms and diagnoses in children (Flanders et al., 2007; Golden et al., 2005; Zito et al, 2003, Zito et al., 2008a). Of particular concern in the US is the high rate of polypharmacy and off-label use of medications in the absence of high quality evidence (Zito et al., 2008a). This has been documented in very young children who have not received appropriate mental health evaluation (Olfson 2010, Eggers 2010). High rates of non-specific polypharmacy in foster children (Zito 2008b) deserve special consideration. Foster children usually have experienced significant abuse, neglect or loss, so are potentially more vulnerable to stress-related disorders; and tend to have a higher risk of intra-uterine toxicant exposure, again increasing risk for disorders related to these exposures. Additionally, they are likely to lack family with intense emotional investment in them, leading to medical decisions that may not be in the child’s best interest. It is under these difficult circumstances that the clinician must be especially mindful of best practices.

Cultural and societal influences on medical decisions
In the US, rates of psychopharmacology to treat behavioral symptoms are 2-3 times greater than in Western Europe (Zito et al, 2009), suggesting cultural values are playing an important role in our medical decisions. Some have argued that it is prejudicial to patients to consider values when discussing psychiatric care (see Resko Sidebar in Parens and Johnston, 2011). However, the EBM Workgroup contradicts this point, stating “acknowledging that values play a role in every important patient care decision highlights our limited understanding of eliciting and incorporating societal and individual values.” (Guyatt et al., 2000 p.1292). Even in a clinical situation as straightforward as the use of antibiotics to treat infection, the decision to treat and how, will depend on patient, context, and values (Ibid).

Children’s psychiatric and developmental disturbances are common and have significant potential to impact function and learning (Centers for Disease Control and Prevention, 2009, 2008; Merikangas et al., 2010), bringing a sense of urgency to our task as diagnosticians and pharmacologists. Unfortunately, several large, cultural and societal issues have impinged on our work and cannot be ignored,
despite our intention to adhere to best practices: These include the dramatic changes in managed care and the insurance industry, which have sharply limited child and adolescent psychiatrists’ (CAP’s) contact with our patients (Jellinek 1999); drastic budget shortfalls in community mental health settings, such that therapy often is done by providers who are inexperienced and in transition; a decrease in funding to social institutions that non-specitically support healthy development (such as social services, public schools, libraries, parks, recreation programs, community police programs, environmental protection etc); and intense economic pressure on parents, leading to anxious and fragmented families. If these factors are, as seems plausible though unproven, reducing our ability to care for children at risk for mental illness, then psychiatrists find themselves faced with a dilemma posed by Murray: is it right to “look for medical solutions to social problems?” (Murray, 1996).

Treatment Issues
There is substantial evidence linking early stressors with negative mental and physical outcomes. These stressors include exposure to poverty, trauma and abuse, lack of stimulation, poor nutrition, and exposure to toxicants (Amon-Polak et al, 2009; Felitti et al., 1998; Greif Green et al., 2010; Dolinoy et al., 2007; Slopen et al., 2010; Landrigan et al, 2010). As a medical specialty that is specifically trained to treat the mental sequelae of adversity, it is unreasonable for us to give it short shrift in our work with children. Increasing evidence for the effectiveness of various psychotherapies is emerging; integrating this approach in our assessment and treatment with impoverished and at risk children and families, is good medical practice.

In the case of children’s psychiatric symptoms, there are few, if any, objective physical markers that reliably distinguish different entities, especially in the clinical setting (Zito et al., 2008a). Putting it broadly, children usually present with a fairly narrow range of symptoms, but have an enormous heterogeneity of antecedents for their disorders. To pick a common example, severe tantrums can exist in the setting of developmental disorders, posttraumatic stress disorder, bad behavior, fatigue, attention deficit hyperactivity disorder, hypoglycemia, etc. Algorithms or reimbursement policies that limit psychiatric evaluations to the use of symptom checklists can lead to premature diagnosis.

The MTA (MTA, 2004; Attention Deficit Hyperactivity Disorder, ADHD) and TADS (TADS Team, 2004; Adolescent Major Depressive Disorder, MDD) studies stand out as large, multi-site, longitudinal RCT’s combining therapy and medications for children’s syndromes that are commonly accepted as providing meaningful clinical information. In each of these studies, medications reliably provided relief of symptoms, but the reporting of long-term results of the MTA were nuanced and careful. Even with this data, many families decide not to use psychotropic medicine in deference to their values. To add to our difficulties, numerous studies suggest that children’s psychiatric symptoms often can be significantly impacted by external factors. For example, treating parental depression also decreases psychiatric...
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symptoms in children (e.g., Weissman and Olfson, 2009; Vidair et al., 2011). It is also the case that not every individual responds to a generally effective treatment. For these reasons, clinical skill and professional experience remain necessary for wise medical decisions (Guyatt et al., 2000).

In sum, child and adolescent psychiatrists have found themselves caught between multiple rocks and hard places, as they balance the urgency of symptoms and the distress of families, decreased contact with patients, inadequate access to care, studies that do not match their needs, and dysfunctional social systems. (Parens and Johnston, 2011). In this setting, a methodical approach is paramount. Bioethics clarifies our goals, and helps us balance competing moral obligations. The basic principles remind us to be transparent, thorough, and collaborative as opposed to paternalistic. While some children's disorders can be life long (Copeland et al., 2011), many resolve without intervention (Angold et al., 2000). Periodic re-evaluation and adjustment of treatment is absolutely necessary.

Case examples
Four imaginary cases will demonstrate the application of these principles. (Any resemblance to real patients is due to the frequency of these situations.)

1. Parent with intense psychological projections on a child: Medical indications, Mutualism.
Rita has recently emerged from an abusive relationship, and is living with her stable but emotionally uninvolved and unsupportive parents. She presents to a community clinic with her 7-year-old daughter Anne, complaining that Anne is aggressive and “crazy like the ex husband.” Rita admits that during her pregnancy, she smoked cigarettes, was depressed and often ate poorly. Anne was never abused, but commonly witnessed domestic violence. She currently is failing in school.

Anne clearly has a number of risk factors for emotional disturbance. However, her mother is more focused on her own personal distress and is unable to recognize that her daughter may be as traumatized as she is. Thus, the establishment of mutualism should be as paramount as an individual diagnosis for Anne. The evaluation needs to assess not just her presenting aggression and potential genetic risk, but also intra-uterine exposures with risks for ADHD and learning disability, current anxiety or PTSD, and impaired attachment with her distressed and struggling mother. Medication may be helpful, but should be chosen specifically and hierarchically, and only in conjunction with appropriate therapies. For example, Child-Parent Therapy (Lieberman and Ghosh, 2006) is an evidence-based intervention that specifically addresses negative projections on their children of mothers emerging from violence. Cue Centered Therapy (Carrion and Hull, 2010) is another promising, methodical approach that incorporates family and individual therapy for traumatized children. Other reviews have demonstrated the importance of treating parental psychopathology to decrease children’s emotional disturbances. (Gunlicks and Weissman, 2008; Weissman and Olfson, 2009). A comprehensive learning
evaluation is also required, as problems with processing or expression may be contributing to Anne’s school struggles or fueling intense frustration.

Medication choices need to be guided by short-term urgency—for instance, are Anne’s behaviors life-threatening or just really annoying?—and also by long-term potential risks and benefits. Clinicians must write prescriptions with the understanding that even highly competent parents will sometimes use medications as prn’s without medical consultation, and often inappropriately. Effects can range from unnecessary cognitive slowing to agitation or delirium to dramatic changes in blood pressure to serious cardiac events. Physicians must make sure that parents are fully aware of the medical risks of their children’s drugs, that there are no excessive requests for refills, and that parents are capable of medical follow-up, including EKGs, blood tests, vital sign checks, etc. (Dell et al., 2008). In any situation where there is a potentially lethal outcome, the risk must be balanced against substantial benefit. Parents should be provided with medication worksheets to monitor side effects, and dosing schedules should be kept as simple as possible. It is not realistic to expect a chaotic family to be able to provide the careful medication routine and monitoring available in a licensed program. Parents and, if developmentally appropriate, child must be completely informed. Physicians should under no circumstances be afraid of vetoing a treatment plan if they have come to believe that a family cannot follow up safely. It is tempting to accede to a family’s demands in this type of situation because “they’ll just go somewhere else and get worse care.” This type of pressure should not cause us to act in ways that are inconsistent with our best practices.

2. A teen who would like medication support in the face of parental opposition: Patient preference and mutualism

Brendan is a 13-year-old who has been in trouble at school since kindergarten. His teachers have consistently told parents that he is bright but probably has ADHD. His parents have disagreed with this assessment and removed Brendan from a number of schools. He is in a class for children with “serious emotional disturbance” that fails his academic needs. Now Brendan presents for a psychiatric evaluation after becoming depressed and expressing suicidal ideation. He has been researching ADHD, and is sure that if he had medication and treatment, he would be able to be part of a regular classroom and have a more enjoyable life. He is angry and alienated from his parents, who insist that he is just “bad”. The psychiatrist agrees that he has ADHD, and that his depression is due to inadequate treatment for ADHD as well as a reaction to his parents’ difficulty in understanding his experience.

Some families are ideologically or culturally opposed to the use of psychotropic medication in their children, even when it seems clearly indicated. In the absence of frank abuse or neglect, a psychiatrist’s first step may need to focus, again, on re-establishing (or establishing) mutualism. Building a relationship with parents includes understanding their perspective while helping them understand both their teen’s experience and potential benefit from medical treatment. Interpersonal therapy (Mufson et al., 2004) has a helpful, evidence-based model for helping
depressed teens negotiate role transition with parents. Attempts to force the issue may drive families away. However, a teens’ ability to articulate his experience and negotiate with parents may bring them a greater understanding of his competence and judgment. In such a case, it is also likely that the years of conflict have negatively impacted parent-child communication and left residual patterns of maladaptive behavior on all sides. These will probably need to be addressed as part of effective therapy.

3. Foster child in a chaotic environment, medications as an attempt to rescue a deteriorating situation: Patient preference, quality of life, contextual features

Fifteen-year-old Charles had been living in a group-home for seven years, after removal from his very abusive family. He has no other relatives. He has had consistent behavioral problems but has not had mental health care until now. He was close to the group-home owner, calling her “mom.” However, she is closing the home after a heart attack, and Charles has been placed in a new facility with older teens. She has made no substantial commitment to ongoing contact with Charles. He became hostile, refusing to go to school, destroyed property and threatened to kill himself. He has been hospitalized and diagnosed with major depression and oppositional defiant disorder. The psychiatrist has been told by Charles’ public insurance that he has only three days to stabilize the boy’s behavior, and the psychiatrist’s appeal has been rejected. Charles is no longer an immediate danger to himself, but remains at high risk of returning to his suicidal state in the absence of structure and ongoing therapy. Charles would like to stay in the hospital. The psychiatrist would like to avoid sending Charles to residential care, which would mean moving him to a new county and environment. The new group home will not take him back until he is not aggressive. Charles remains impulsive and his moments of insight are punctuated by hostility or withdrawal. Charles is refusing antidepressant treatment. Under such circumstances, common but ethically questionable solutions have included using a sedating medication such as an atypical anti-psychotic to quickly reduce acting out, or diagnosis “upcoding” in order to increase the chance of a longer hospital stay (Flanders et al. 2007; Blader and Carlson, 2007).

The CAP is being unreasonably asked to remedy a series of misfortunes and social failures. Principles of respect for dignity indicate that the CAP must clearly articulate the dilemma to Charles. On the one hand, he is of an age where he can start participating in medical decisions. On the other, his emotional experience of outrage, hurt or loss may interfere with his capacity to make a good judgment. Charles’ refusal to take a medication may represent his only mechanism of asserting his dignity in the face of all that has happened. Teens may also refuse antidepressant treatment, arguing “if you’d been through what I’ve been through, you’d be depressed too.” There is no easy answer in cases like these. Charles should be fully informed of the medical risks, as well as potential positive outcomes, of all medication choices. If the CAP acknowledges the reality of the situation, and uses therapeutic techniques to help the patient apply reflection and deliberation to his intense feelings, he is at least modeling patient-centered, ethical behavior. Most
clinicians might agree that an anti-depressant could help Charles. Many teens find
some instant relief to their intense dysphoria when taking an antipsychotic.
However, it is not clear that distressed teens can take into consideration the long-
term effects of the medications, given the high stakes of the current decision.
Furthermore, the treating psychiatrist most likely will have no control over Charles’
experience once he leaves the hospital. Unless Charles is to receive adequate
psychiatric follow-up, it may not be safe to discharge him on medication; and due to
lack of relevant studies, it is not clear that the benefits of antidepressants outweigh
the risks in this specific situation.

States will vary in the legal representation and degree of decision-making they
provide to foster children. In the best of circumstances, Charles will have a lawyer
and potentially an advocate who can participate in decisions, or fight to obtain a
longer hospital stay. The psychiatrist can also refuse to discharge Charles,
regardless of medical necessity and reimbursement.

4. The patient who is taking multiple medications without prior adequate
evaluation: Medical indications, quality of life, patient/parent preference.
Danielle is 12 years old. Her family has recently moved from another state. She is on
5 medications for bipolar disorder (including antipsychotics, a stimulant, and
anticonvulsants). Her family reports that all of these are absolutely essential, that
her unmedicated behavior was disorganized and aggressive. They are financially
stressed and both parents work full-time, making it challenging for them to bring
Danielle weekly. Danielle was first treated for ADHD but failed to respond to
stimulants alone. A series of different medications were added to her regimen by a
pediatrician who did not discuss either alternative treatments or potential risks
associated with each medication. She has had no EKG or baseline labs, is obese,
socially isolated and doing poorly in school. Her family is wary that the psychiatrist
will try to change her regimen. Apart from the obesity, they deny any side effects,
and are unconcerned by her poor school performance. They are affectionate with
Danielle, although their ideas of what is developmentally appropriate differ from the
CAP's.

Clearly the first three steps (which need to be taken simultaneously) are to create a
collaborative relationship with her parents, make sure there is no imminent
physical harm to Danielle, and initiate a careful evaluation including, if possible, past
records. Significant lab abnormalities can lead to an immediate discussion of
medical risks. However, lacking a program such as a hospital where Danielle could
be carefully taken off some or all of her medications to assess her baseline function,
the CAP should create a treatment plan that includes psycho-education and a safe,
methodical approach to decreasing these medications. Weekly appointments may
be necessary for some period of time, in spite of the parents’ resistance, to allow the
psychiatrist to develop an alliance with the parents, and reinforce the need for
medical evaluation. While compromise may be necessary, the psychiatrist may
ultimately need to impose a deadline for resistant parents. Weekly contact with
Danielle herself will allow the psychiatrist to form an accurate understanding of her
actual diagnosis. Lacking prior psychiatric work-up, the CAP cannot know whether she has a chronic, major mental illness, a developmental disorder, an anxiety-based illness or some combination thereof. Skillful attention to the parents’ realistic fears and constraints, accompanied by recurrent explanations of potential medical risks, and the cognitive impact of sedating drugs, is likely to help parents participate more actively in Danielle’s care. They may find help from community or on-line advocacy groups and be brought into a position of greater involvement in medication decisions. Once Danielle’s diagnosis is clear, appropriate non-pharmacologic therapies should be included.

**Additional actions**
As physicians, we have been given enormous privilege to share our patients’ lives, and our words and actions often have greater impact than we acknowledge. Some ways that we can advocate for our patients include building consensus with our colleagues, through face-to-face or online discussions (protecting confidentiality); participating in American Academy and Regional Organizations of Child and Adolescent Psychiatry forums; writing letters to editors of journals; and collaborating with patient and parent groups. We can ask the institutions we work for to implement evaluation and treatment protocols that incorporate best evidence. We can educate our families and help them take charge of what may be life-long disability. We must talk to our academic institutions, asking them to design studies that meet the needs of our clinical populations. We can work to translate high quality studies directly into “primary care” psychiatric settings in our day-to-day work.

**Addendum 1**
Adapting the Four Topics Method to Pediatric Psychopharmacology

Synthesised from:

1. **Medical Indications: Diagnosis, Beneficence, Non-maleficence**
   - Have you taken enough time to get an accurate diagnosis? Do you have a plan for re-assessment after a limited period of treatment?
   - Are symptoms acute? Immediately dangerous or chronically troublesome?
   - Are parents responding to symptoms or seeking help in a developmentally appropriate manner?
   - What are treatment goals: long-term wellness or short-term sedation? Flourishing of child and family? Or compliance by child in situation of adversity?
   - How sure are you of your treatment recommendations? What is evidence base for the child’s condition? Are other therapies also in place?
   - What are the medical consequences of treatment? Will the child and family be able to manage these?
Is refraining from medicating safer than medicating?

As part of obtaining informed consent, physicians should go over serious adverse drug events (ADE’s), and encourage parents to learn as much as they can about the medications. Inviting parents to be active learners develops the therapeutic alliance. (For instance, giving patients and families the homework assignment of doing an internet search on their medications often helps them understand the medicines more than reviewing a standard handout with them.)

Physicians are responsible for ensuring that families will obtain and follow standard monitoring practices: Height and weight, vital signs, EKG’s, blood tests, close follow up for obesity, as well as observation for acute and serious adverse drug events. Physicians can provide monitoring handouts, and review them at every visit (Dell et al, 2008). If families are not able to do so, the risks for adverse events increase, and need to be considered in ongoing renewal of medications. Psychiatrists should communicate regularly with primary care physicians.

2. Mutualism and Respect for Human Dignity

- Is the parent able to make an informed decision? Consider the parent’s immediate distress, psychological projections, beliefs, level of education, personal mental illness, prior contact with mental health, cognitive capacity and other issues that might unduly influence judgment.
- Have you completely informed the parents about risks involved with the medications, and the medical follow up needed?
- Have you fully discussed current controversies within the field regarding diagnosis and medications?
- Is the parent invested in understanding the child’s experience and increasing mutualism, or simply in increased compliance? Are there other institutions pushing for medications (schools, other care-providers)? Have their agendas been analyzed?
- What does the child want? How does the child experience the use of medications? (Does it signify she is branded as damaged, or that her distress has been understood and the goal of treatment is to facilitate growth?)

3. Quality of Life

- What are prospects for return to meaningful life with and without treatment? Is there evidence that the treatment you are offering actually improves long term outcome?
- What are realistic treatment goals? What long-term harms should be expected with and without treatment?
- Are all other supports and therapies either in place or in planning?
- Do you have a timetable for reducing and re-evaluating medications?

4. Contextual Features:

A: Medical establishment or the individual institution as sources of bias
How are reimbursement practices influencing care? (Shortening assessments, increasing pay for use of medications—hour of psychotherapy vs 30 minutes for medication)

Are there unintentional biases, including unconscious investment in a specific treatment, or in a specialty clinic with an academic reputation?

Is clinical research or teaching impacting treatment decisions?

Are treatment guidelines free from conflict of interest, (for instance were they developed with pharmaceutical support, or by physicians with pharmaceutical relationships that have not been adequately examined?)

B: Cultural and family factors influencing decisions:

Are families able to afford medications? Are there generic options?

What are the cultural and societal factors influencing treatment decisions, including distrust of psychiatry, or a prior negative experience?

Are there problems of allocation of resources? Is the child getting optimum non-medical therapies regardless of economic pressures?

C: Social determinants of adverse outcomes

Stress, poverty, and the attendant health risks (malnutrition, lack of early age appropriate environmental stimulation, exposure to environmental toxicants, diminished opportunity, parental and community demoralization) are major contributors to children’s psychiatric symptoms. How is your individual work with each child addressing these issues?

Addendum 2
Evaluating Published Studies for Quality and Relevance

A search on the Cochrane database, done at the end of 2011, revealed the following: excluding the diagnosis of autism, there were only three medication studies for children with behavioral disorders. They were as follows:

1. Anticonvulsants: A meta-analysis of all studies (including all languages) of acceptable quality (randomized, placebo-controlled, prospective) concluded that there was insufficient evidence. Of note, this review included adults as well as children. While there was a finding that sodium divalproex was superior to placebo for youth with conduct disorder, there were no overall positive recommendations for anticonvulsants in youth. (Huband et al, 2010)

2. Atypical antipsychotics: The authors were unable to find any studies of sufficient quality to be included in a review of risperidone for ADHD and intellectual disabilities. (Thomson et al, 2010)

3. Stimulants: There was only one study of sufficient quality to be included in a study of amphetamine for ADHD in children with intellectual disability. This one
study failed to show benefit, and the treatment caused increased side effects. (Thomson et al, 2010, b).

What makes a good study, according to the Cochrane reviewers and the GRADE group?

**Treatment Studies:**
- Is the objective of the study clear, specific, and clinically relevant?
- Is the diagnosis biologically plausible, and valid? Of great importance is the fact that a cluster of behaviors is NOT equivalent to a medical diagnosis, as discussed above.
- A prospective, randomized controlled, double blind study is superior to an open-label observational study or a retrospective chart review.
- Studies should be of sufficient duration to detect negative outcomes as well as long-term positive benefits.
- Of greatest concern in child psychiatry, is the lack of specificity of most trials for behavioral disorders: are authors simply documenting sedation for a heterogeneous group of children with disruptive behavior, or a beneficial medicine for a specific psychiatric illness?
- Is the study population sufficiently similar to general clinical populations to allow for general clinical use of findings? For example, a small cluster of children in a tertiary care institution who have failed other treatments, is very different from community populations for whom comprehensive care is hard to access.
- If authors have financial relations with the funding pharmaceutical company, readers must be able to analyze the findings for risk of bias. Simple disclosure of financial relations is insufficient. (See also Morin et al., 2002)
- Any risk of bias, especially financial stake in outcome, reduces quality of study.

**Meta-Analyses**
- A meta-analysis should include all languages, positive and negative findings, and if unpublished studies are included, then both positive and negative studies must be included.
- The inclusion of low-quality studies diminishes the value of a meta-analysis; the presumption is that only quality studies are included in the first place.
- Authors who write meta-analyses of their own studies must include independent co-authors; it is preferable to have authors of meta-analyses who have NOT published included studies of a specific treatment.
- At this point, there are insufficient, quality studies to allow us to use the GRADE criteria to go from study to treatment recommendation. Given the high rate of psychopharmacology in children, it is clear that we urgently need to adopt guidelines for rating studies, and need to publish systematic reviews and meta-analyses that meet GRADE and Cochrane criteria, so that we can generate them.

**Sources:**
- Cochrane Library and Handbook:
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- **www.cochrane-handbook.org.** Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0

**GRADE**

**Bioethics and Psychopharmacology References**


Berenson, A., Eli Lilly said to play down risk of top pill. N.Y. Times, 12/17/06.

Note: This topic is covered in detail in endocrine journals, but has not been sufficiently discussed in psychiatry. Many primary care doctors who prescribe SSRI’s are also unaware of this risk.


Note: The exploding literature of epigenetics makes it very clear that creating healthy environments constitutes a biologic intervention, and must be given great weight in making treatment recommendations.


Note: This important, ongoing set of studies places early trauma squarely in the medical field as a major medical risk factor. The ACE inventory is available on-line through Google.


Note: This replicates the findings Felitti et al, that there is a powerful association between early trauma and psychiatric disease.

Note: A number of interventions strongly suggest that directly addressing parental mental health is beneficial to children's emotional/behavioral symptoms. Other studies will be starred.


*Hollis, C and Thompson, A. Acute dyskinesia on starting methylphenidate after risperidone withdrawal. Pediatric Neurology.2007; 37: 287-288. Note: If one thinks mechanistically, one can understand why giving a dopamine agonist to a child whose DA receptors are upregulated due to antipsychotic use is risky. The worst case of TD I have ever seen was in a 12 year old who had been treated with this all-too-common combination of antipsychotic plus stimulant.


The field will hopefully learn from this case history of fraudulent marketing of a medication for psychiatric illness.


*Parens E. and Johnston J. Troubled Children: Diagnosing, Treating, and Attending to Context. Special Report Hastings Center Report 41.2011;no.2:S1-S32. Note: This report outlines the challenges we are facing, although does not reach any firm conclusions. (Disclosure, I was a participant)
Note: Another important red flag.


This is one of a number of very important epidemiological studies by this group. I highly recommend a PubMed search of Zito, Julie.


*Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, Cognitive-Behavioral Therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial. JAMA.2004;292(7):807-820.

This is an excellent potential model for our field.


