Pediatric psychopharmacology: too much and too little

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Rapoport's lucid overview points to overmedication in children in the USA, especially for attention-deficit/hyperactivity disorder (ADHD) and irritability. By contrast, many countries make so little use of medication that it seems probable that children who could profit do not receive it. Undertreatment is perhaps a bigger problem globally than overmedication.

In Europe, stimulants are used increasingly, but rates are very much lower than the 73 per 1,000 in the USA that was described by Angold et al (1) in 2000. In a UK national database report from years 2003–2008, the prevalence rose from 4.8 to 9.2 per 1,000 in the 6–12 age range, and from 3.6 to 7.4 per 1,000 at ages 13 to 17 (2). In France, the rate was 1.8 per 1,000 in 2005 (3). In Italy, stimulant use was almost unknown until a few centres were recently licensed to prescribe. In all these countries, preschool use was too rare for an accurate estimate. As to other types of medication, some (e.g., antipsychotics in schizophrenia) are uncontroversial; others (e.g., antipsychotics for irritability) are used much less in Europe than in USA. What factors influence these startling differences?

A first factor is availability of prescribers. Rapoport emphasizes the market forces confining US psychiatrists to "medication clinics"; if some clinics use only medication for ADHD, one must doubt whether adequate practice is being followed. By contrast, parent training is widely available and free in the UK, while prescribers are in shorter supply – which may well limit the need for, and the use of, medication. In many countries, lack of child psychiatric services in general, and of professionals qualified to prescribe in particular, restrict all therapeutic services

including medication. Good training of paramedical staff could allow both medication and behavioural interventions to be included in therapy.

A second factor is perceived efficacy of drugs and alternatives. In some low-prescribing countries, non-pharmaceutical interventions are regarded as more or less equivalent to drugs. European Guidelines and those in the UK from the National Institute for Clinical Excellence (NICE, 4) recommend both medication and psychological approaches (especially behavioural) as being effective and cost-effective, at least for cases of mild or moderate severity. Similarly, UK guidelines for the treatment of childhood depression recommend that selective serotonin reuptake inhibitors should only be used after three months of psychological therapy – advice that has perhaps been outdated by recent studies arguing that the combination of both is more effective and safer than either treatment alone.

Furthermore, a recent meta-analysis of non-pharmacological interventions in ADHD casts some doubt on the value of treatments such as behaviourally oriented parent training – and indeed most dietary interventions (5). Evidence for efficacy depends on ratings from parents who have themselves been involved in delivering the therapy, and may therefore not be unbiased. Teacher ratings and assessments by blinded observers suggest much smaller effect sizes. This does not, of course, mean that parent-delivered therapies are useless. Even if the good effects are situation-specific, and even if they represent more positive parental attitudes rather than a profound change in the children, they may still be very worthwhile.

Nevertheless, there may need to be some re-evaluation of the power of medication relative to psychological interventions. If, in line with European

recommendations, medication were to be provided for most of those with the World Health Organization's definition of hyperkinetic disorder (about 1% of school-age children) and those children with ADHD that falls short of hyperkinetic disorder (about 4%) who fail to respond to behavioural interventions (perhaps half of that 4%), then there would be approximately 30 per 1,000 children eligible for treatment. Of course, not all children would or should be presented for treatment, but it is hard to escape the conclusion that countries such as England and France are using less psychopharmacology than would be optimal for child health.

A third factor is cultural. The perceived overuse of medication in the USA has generated widespread media criticism in Europe, amounting in some cases to hostile campaigns against individual doctors. The fire is fed by opposition to biological psychiatry, e.g., from sociological and psychoanalytic perspectives and from anti-American political positions. The resulting polarization can get in the way of balanced and discriminating use.

A fourth factor is represented by adverse effects. Differing perceptions of drug dangers influence regulatory authorities and prescribers. Clozapine, for instance, is statutorily regulated in some countries for its haematological risks; in others, such as some ex-Soviet countries, it may be prescribed in the same way as other antipsychotics. The metabolic and obesity-inducing effects of second-generation antipsychotics are sometimes taken to debar their use for non-psychotic aggression in all but the most severe cases (6), while their wide use for this purpose in parts of the USA implies that they are considered to be manageable with low doses and good monitoring.

Detailed European recommendations for ADHD based on systematic review (7) have indicated that the hazards of stimulants are few and manageable. Oral

administration (especially of extended-action preparations) is unlikely to lead to misuse. Nevertheless, the fear of inducing dependence has led some countries to limit availability.

A final factor is uncertainty of indications. Most of the problems of child mental health are distributed in the population as continuous dimensions. It is therefore a real difficulty to decide where to place cut-offs for the use of medication, or how to decide on the balance between medication and psychological therapy. For ADHD, NICE (4) used a reanalysis of a large US trial to recommend a cut-off for the use of medication as first therapy, corresponding to the ICD-10 definition of “hyperkinetic disorder” (severe, pervasive and impairing ADHD).

In summary, great international differences in the use of psychopharmaca stem from professional and cultural attitudes. The evidence base on clinical outcomes should be extended and applied.

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What's next for developmental psychiatry?

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J. Rapoport provides an accurate and thoughtful overview of the history and current state of pediatric psychopharmacology. Since Bradley's report in 1937 concerning the use of benzedrine in children with behavior problems (1), pediatric psychopharmacology has been with us. However, psychoanalytically oriented psychotherapy was the generally preferred treatment for children and adolescents in the USA until the late 1970s, when things began to change. By 2002, with the publication of the first edition of *Pediatric Psychopharmacology* (2) and the advent of *Journal of Pediatric Psychopharmacology*, the use of psychoactive medications in children had become main stream in the USA, although remaining problematic for large segments of the general population in Europe and other areas of the world, including South America.

There is no doubt that for many children the use of psychoactive drugs has been beneficial. So, from my perspective, pediatric psychopharmacology is here to stay. Rapoport

summarizes many of these advances. Sadly, however, there are many children for whom the benefits are modest at best.

We need new agents, but the pharmaceutical industry has become cautious. For the most part they are content to develop analogs of successful compounds. How many derivatives of stimulant medications are on the market, to say nothing of the serotonin reuptake inhibitors and antipsychotics?

As noted by Rapoport, attempts at “repurposing” of existing compounds initially developed for other indications also make sense. Here, it is of interest to recall that antipsychotics were first developed by surgeons to potentiate the effects of anesthetics and analgesics, and cycloserine was initially used as an antibiotic to treat tuberculosis.

A significant portion of my research and clinical practice is focused on Tourette's syndrome (TS), where we do not have ideal agents (efficacious with minimal side effects). Consequently, we are in the midst of trying a number of agents, some of which are novel and others have been in development for other indications. For example, recent genetic findings indicating a

role for central histamergic pathways (3,4) have led to the development of a clinical trial for histamine H3 receptor antagonists, using an agent first developed for the treatment of obesity. We are also evaluating the evidence base for the use of nutritional supplements. Caution is warranted here as well. Once nutritional companies recognize the commercial potential of their products, financial as well as clinical pressure will likely drive the development of ever more aggressively marketed products.

More importantly, we need to develop and sustain efforts to build on the strengths and interests of children and adolescents with behavioral and emotional difficulties and find ways to take advantage of advances in developmental neuroscience to enhance their cognitive and emotional development. This echoes the recent forum in *World Psychiatry* on “Positive mental health: models and clinical implications” (5). When seeing a new case in our clinic, I frequently ask the parents “to brag” about their child and indicate what his/her favorite activities are and what skills he/she is developing. In the case of TS, engaging in activities that require