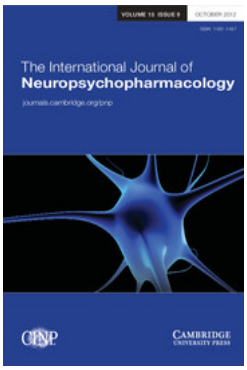

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SPECIAL SECTION

Advances in paediatric neuropsychopharmacology: an overview

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Abstract

This Special Section of the *International Journal of Neuropsychopharmacology* highlights current progress in paediatric neuropsychopharmacology. Combining critical reviews and, in some cases, new data, specific topics include: biological findings in major depression, sleep dysregulation in depressed youth, cardiovascular and ventilatory dysregulation in panic disorder, paediatric autoimmune neuropsychiatric disorder associated with strep (PANDAS), age of onset as a subtype marker in tic and obsessive–compulsive disorders (OCD), functional and pharmaconeuroanatomy of OCD and the behavioural pharmacokinetics of methylphenidate. In this introductory section, these articles are placed in the context of the state-of-the field and, more specifically, within the framework of recent NIMH initiatives in paediatric neuropsychopharmacology.

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Key words: Neuropsychopharmacology, child, adolescent, NIMH, treatment, diagnosis, PANDAS.

Introduction to the Special Section

While much remains to be learned (Jensen et al., 1999b; Vitiello, 1998), it is clear that the revolution in behavioural neuroscience that has transformed adult psychiatry is now reaching across stages of development to encompass child and adolescent psychiatry (Hyman, 2000). In fact, many adult psychiatrists are pursing collaborative relationships with paediatric colleagues precisely because the epidemiological data now suggests that adult mental illness has its roots in childhood, which implies that early identification provides an opportunity for prevention of lifelong neuropsychiatric morbidity and mortality (Vitiello and Jensen, 1997). Much work remains to be done before promise becomes clinical practice (Norquist and Hyman, 1999). This Special Section of *IJNP* arose as an outgrowth of discussions concerning recent progress in paediatric neuropsychopharmacology between one of the guest editors of the Special Section (Dr March) and the Editor of *IJNP* (Professor Bernard Lerer) at the 1999 Regional Meeting of CINP in Asuncion, Paraguay. While not even remotely comprehensive – recent textbooks provide a more detailed yet already out-of-date view of advances in paediatric neuropsychiatry (Coffey and Brumback, 1998; Harris, 1995) – the Special Section should introduce the reader to some of the newer and more interesting developments in behavioural neuroscience that inform modern paediatric neuropsychiatry.

Considerable research among adults implicates poor regulation of emotional responses in risk for various cardiovascular diseases. Much like many psychiatric disorders, some cardiovascular diseases are considered developmental conditions, with their roots in childhood (Gerber and Stern, 1999). Among adults, deficient regulation of the autonomic nervous system has been linked to both emotional disorders and cardiovascular conditions. Research specifically documents an association between panic attacks and sudden death in adults (Gorman and Sloan, 2000). As abnormalities in heart period variability are linked to both sudden death and acute episodes of anxiety, such as panic attacks, abnormalities in heart period variability may at least partially explain associations between some emotional and cardiovascular conditions. In this context, Catherine Monk working in the laboratory of Danny Pine, formerly of Columbia University and now heading the paediatric division of the

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newly formed NIMH intramural Program in Mood and Anxiety Disorders headed by Dennis Charney, examines the association between paediatric anxiety and autonomic dysregulation, as reflected in heart rate variability profiles (Monk et al., 2001). In children, as in adults, they report that anxiety is associated with subtle abnormalities in autonomic regulation. Such findings carry implications for developmental models of both cardiovascular as well as emotional disorders. In turn, this suggests that the relationship between childhood anxiety and adult panic is nosologically complex or, stated differently, that the 30 year effort to force adult diagnostic criteria downward in age to children and adolescents is fraught with problems, especially given the high rates of comorbidity among childhood onset anxiety disorders (Angold et al., 1999).

Beginning with the pioneering studies of Kim Puig-Antich (Geller and Ryan, 1992), no centre has contributed more to the understanding of biological factors in paediatric affective illness than the Child Psychiatry Group at Western Psychiatric Institute and Clinics (WPIC). Summarizing 30 years of progress, much of it at WPIC, and introducing new information regarding dysregulation of growth hormone regulation in youth at risk for depression, Pedro Heydl and Boris Birmaher review the literature on biological markers in paediatric depressive disorders (Birmaher and Heydl, 2001). Their summary of neuroendocrine, serotonergic and sleep probes suggests that, while there are unique developmental, age, severity, and exposure to stress factors that alter the nature and course of affective illness in youth, the psychobiology of childhood depression is not all that dissimilar in the aggregate from that seen in adults.

With Birmaher and Heydl's review providing a heuristically valuable and historically important context, Graham Emslie and colleagues from the University of Texas, Dallas Southwestern, then go on to provide a state-of-the-art summary of the literature on sleep in depressed children and adolescents, concluding that depressed children and adolescents exhibit less sleep continuity and non-REM sleep differences in comparison with control subjects than do adults (Emslie et al., 2001). Importantly, they note that results from adult sleep polysomnography studies cannot necessarily be generalized to children and adolescents. They then provide new data suggesting that sleep continuity variables, specifically sleep efficiency and prolonged sleep latency, are more disrupted in youth who exhibit early recurrent depression than those who remain well. As recently as 1998, Harrington and colleagues comment with specific reference to depression that 'the focus remains on treating ill youth and likely will until further research offers us the opportunity of more targeted prevention' (Harrington and Clark, 1998). Once replicated and extended, the work by Emslie et al. (2001) offers the promise of readily available clinically relevant polysomnographic markers for both length of treatment and perhaps even the need for long-term pharmacological treatment in depressed youth.

As in adults, OCD in youth is a relatively common and chronically disabling illness that typically begins in childhood and extends into adulthood in as many as two-thirds of all cases (March and Leonard, 1996). Several lines of evidence suggest that age of onset (early vs. late) or comorbidity, especially with the tic disorders, or both, may represent in phenomenology a neurobehavioural subtype of OCD (Zohar, 1999; Zohar et al., 1997). In a large sample of clinically referred youth with OCD, Geller and colleagues (Geller et al., 2001) provide evidence that externalizing, tic and anxiety disorders, but not mood or psychotic disorders, show an early onset pattern associated with OCD. Taking a different perspective on early onset OCD, Henrietta Leonard formerly at the NIMH and now at Brown University and Sue Swedo, Director of the Pediatrics & Developmental Neuropsychiatry Branch at the NIMH, summarize their exciting albeit controversial (in the sense that all truly interesting science is controversial at the outset) attempt to define an infectious disease model for early onset OCD (Kurlan, 1998; Leonard and Swedo, 2001; Trifiletti and Packard, 1999). Lead from inception to current understandings by leading-edge researchers at the NIMH (Garvey et al., 1998), paediatric autoimmune neuropsychiatric disorders associated with strep (PANDAS) will likely yield the first empirical demonstration of an aetiopathogenically defined subtype of OCD and tic disorders. Unlike schizophrenia, where neuroimmunological models remain mired in aetiopathogenic controversy (Watson et al., 1999), the evidence supporting the existence of PANDAS (if not its prevalence or phenomenological boundaries) is gaining increasing empirical support. Amazingly, some have even speculated that PANDAS may lead to revision of the Jones criteria for rheumatic fever to include post-streptococcal OCD or tic disorders (Asbahr et al., 1998). Of critical interest to practising child psychiatrists and primary-care doctors, immunomodulatory therapies in investigational protocols show promise in ameliorating symptoms in the most severely symptomatic children (Perlmutter et al., 1999). If replicated, it may be that the secondary prevention of some children with early-onset OCD like that of rheumatic fever itself will depend on antibiotic prophylaxis (Garvey et al., 1999). Furthermore, although open to a variety of methodological caveats, Peterson et al. (2000) recently suggested that the PANDAS phenotype may extend well beyond OCD and tic disorders to just those conditions, especially attention deficit hyperactivity disorder (ADHD) (Peterson et al.,

2000), identified by Geller et al. (2001) in this Special Section as being associated with early-onset OCD.

Information-processing models rooted in the application of cognitive neuroscience to paediatric mental illness are on the horizon across a variety of paediatric anxiety disorders (Pine and Grun, 1999). Staying with OCD, progress in understanding the functional neuroanatomy and pharmacoanatomy of paediatric OCD is farther advanced than any other paediatric neuropsychiatric illness (March and Leonard, 1998). David Rosenberg from Wayne State University in Detroit has been a pioneer in using the tools of neuroimaging, particularly structural and functional MRI and MRS to disentangle the pathobiology of OCD (Rosenberg and Keshavan, 1998). Introducing new data on the impact of treatment on neural function, Rosenberg et al. (2001) describe an integrated series of neurobiological studies conducted largely in his laboratory that provide a developmentally sensitive test of the hypothesis that neurodevelopmental abnormalities of ventral prefrontal-striatal-thalamo-cortical circuits may be involved in and contribute to the aetiology and presentation of the OCD in youth.

With a rapidly growing literature on the pharmacokinetics of other compounds, such as the serotonin reuptake inhibitors (Alderman et al., 1998), it is clear that children and adolescents have much in common but also show interesting differences from adults in drug absorption, disposition, metabolism and excretion (Vitiello and Jensen, 1995). Similarly, an emerging literature on the risk for drug–drug interactions is beginning to inform clinical practice, although much remains to be learned (Leonard et al., 1997). In this regard, because data about drug safety and efficacy in adults can rarely be extrapolated to children, there is no substitute for greatly increased attention to pharmacodynamic (PD) and pharmacokinetic (PK) studies in paediatric psychopharmacological research (Vitiello and Jensen, 1997). Given a wide range of new and reformulated psychostimulants about to hit the ADHD market in the USA and, presumably, Europe (see, for example, Kimko et al., 1999; Modi et al., 2000), and the short time–response profile of most psychostimulants, PK and PD studies of these compounds are of particular relevance to clinical practice (Greenhill et al., 1999). Nonetheless, despite the fact that there is no better studied condition in all of psychiatry irrespective of age than ADHD (Swanson, 1993), we still lack basic PK/PD data on the relationship of stimulant dose, serum level and behavioural/symptomatic outcomes in children treated with methylphenidate, the most commonly prescribed psychostimulant in youth (Jensen et al., 1999a; Kimko et al., 1999). While far from answering this question fully, Greenhill et al. (2001) report a novel PK/PD study of methylphenidate in a sample of ADHD boys. As expected, motor performance errors and dose proved to be inversely related; conversely, while plasma levels and dose were linearly related, plasma level and response were not significantly correlated, implying that the time to maximum concentration (T_{max}) may be more critical than the maximum concentration (C_{max}) itself or the area under the curve (AUC) in predicting response. Importantly, in contrast to recent PD studies suggesting subtle single dose tolerance effects (Swanson et al., 1999), PK and PD parameters did not change between acute and maintenance drug-treatment phases, suggesting an absence of tolerance at least over the intermediate term using conventional dosing strategies.

These are exciting times for paediatric psychiatry. The interplay between clinical practice and research remains rich and varied (Rutter, 1999). Advances in treatment have been sound if not spectacular to the point that most observers now agree that translating research findings regarding treatments that work into clinical practice is the key to improving the public health of mentally ill children and adolescents (Hoagwood et al., 1995). Progress has not only come in psychopharmacology, which now has its own journal, the *Journal of Child and Adolescent Psychopharmacology*, but also in cognitive–behavioural psychotherapy (CBT), which in many cases shows far more empirical support than other available treatments (March, 2000). CBT meshes nicely with developmentally sound neurobehavioural approaches to paediatric mental illness in which psychopathology can be seen as analogous to a learning disability mediated by dysfunction in highly conserved central nervous system information processes. To the extent that symptom relief occurs, it can be assumed that a reduction in symptoms reflects concurrent changes (e.g. learning) in the central nervous system. Looked at this way, the cognitive behavioural treatment of paediatric mental illness can be thought of as partially analogous to the treatment of juvenile-onset diabetes, with the caveat that the target organ, the brain, in the case of major mental illness, requires interventions of much greater complexity. Using OCD as the exemplar, treatment for diabetes and OCD both involve medications, which, in diabetes, might be insulin and in OCD, a serotonin reuptake inhibitor. Each also involves crucial psychosocial interventions that work in part by biasing the somatic substrate of the disorder toward more normal function. In diabetes, the psychosocial treatment of choice is diet and exercise, and in OCD, CBT. Working with Nili Benazon and her colleague, David Rosenberg, we have very preliminary data (unpublished) using MRS suggesting that the pattern of response for children responding to paroxetine may differ from those responding to CBT. If this holds true, then the com-

bination of CBT and pharmacotherapy (but only if supported by evidence from comparative treatment trials) may be more effective than monotherapy alone. While the treatment of OCD and other paediatric neurobehavioural illnesses within the medical model is far from fully realized, the ground has been prepared for an evidence-based approach to both training and clinical practice (cf. the Institute on Evidence-based Medicine that Peter Szmatari from McMaster University in Ontario, Canada, and one of us (J. S. March) conducted at the year 2000 Annual Meeting of the American Academy of Child and Adolescent Psychiatry).

Until recently, the National Institute of Mental Health (NIMH) has supported most of the research conducted in the USA on the biological bases of childhood mental illness and on the effects of treatment and preventive interventions for children and adolescents. Thus, over the years, the NIMH has funded studies in a broad array of conditions, including the efficacy of stimulants and tricyclics in attention ADHD, of tricyclics and fluoxetine in depression, and of neuroleptics in Tourette's disorder. Fortunately, the context of paediatric psychopharmacology in the USA has now substantially changed. In response to enabling legislation (Laughren, 1996), the pharmaceutical industry is now showing greater interest in developing psychotropic medications for paediatric use. Specifically, federally enacted legislation (Food and Drug Administration Modernization Act, November 1997) and new Food and Drug Administration (FDA) regulations (FDA, 1998) have provided powerful incentives to the pharmaceutical industry for studying the effects of medication in children. As a consequence of these initiatives, more than 100 new studies of paediatric age have been started, of which 10 focus on psychotropic medications. Considering the new interest of industry in child psychopharmacology, NIMH has redirected its efforts to areas that remain understudied and still in need of expansion because of their considerable clinical relevance and public health importance. Among these areas are: (1) the study of the effectiveness of treatments (i.e. treatment effects in usual conditions of clinical practice, as opposed to ideal experimental conditions of 'efficacy' studies); (2) the direct comparison of different treatment modalities (e.g. pharmacotherapy vs. psychotherapy vs. combined treatment); (3) research on treatments for disorders such as autism, bipolar illness and schizophrenia; (4) research on treatments for youths with co-morbid disorders; (5) study of long-term effects of treatments on functional parameters of clinical interest; and (6) assessment of safety of treatments, especially over the long term.

One of the major obstacles to conducting multi-site clinical trials in children is the limitation of the research infrastructure. To address this deficit, in the last 4 years, NIMH has established a network of research units devoted to paediatric psychopharmacology. Currently, there are 7 units at qualified academic sites, with several others connected to these units as collaborating sites on various protocols. Three current studies funded on the NIMH-funded Research Units of Pediatric Psychopharmacology network illustrate the point: (1) a study of fluvoxamine vs. placebo in anxious children and adolescents in which approx. 70% of the medicated group and only 30% of the placebo group responded to treatment (RUPP Cooperative Group, In Press); (2) a current treatment addition study of fluvoxamine vs. placebo on top of a stable psychostimulant in ADHD comorbid with anxiety again in children; and (3) an initiative to develop and test an empirically derived patient and clinician report form for ascertaining adverse events.

In this regard, substantial progress in developing psychosocial and psychopharmacological monotherapies has prepared the way for large comparative treatment trials in samples that are reasonably representative of clinical populations seen in clinical practice. For example, the NIMH-funded collaborative Multimodal Treatment Study of Children with ADHD (MTA) addressed a priori questions about the individual and combined effects of pharmacological and psychosocial (behavioural) treatment for children aged 7–9 years with ADHD (Arnold et al., 1997). Treatments that included the MTA medication algorithm – Combination (Comb) and Medication Management (MedMgt) – showed better outcomes than those without, i.e. Behavioural Treatment (Beh) and Community Comparison (CC), on outcome measures involving core ADHD symptoms (MTA Cooperative Group, 1999b). On other outcome measures, the pattern of response was slightly different: for internalizing behaviours, unimodal treatments (MedMgt, Beh) did not differ significantly and, in several instances, Comb proved superior to Beh for internalizing outcomes, whereas MedMgt did not. For example, parent report of a child's anxiety disorder on the Diagnostic Interview for Children moderated outcome for core ADHD, internalizing, and anxiety symptoms (MTA Cooperative Group, 1999a). For participants with anxiety disorders, Beh was significantly superior to CC and no longer different from MedMgt and Comb on some measures. Thus, the presence of anxiety disorder in the MTA sample did not appear to predict a worse response to medication and did predict relatively better response to behavioural treatment strategies. More detailed analyses using hierarchical linear models (Bryk and Raudenbush, 1992) demonstrated that this effect, which was clinically significant and did not depend on the presence of intercurrent conduct problems, probably reflected the impact of Beh on affectively negative behaviours oc-

curring between parent and child (March et al., In Press). Importantly, we are currently conducting NIMH-funded comparative treatment trials in paediatric OCD and in adolescent depression, with the latter – the Treatment of Adolescent Depression Study (TADS; for information, see http://www.nimh.nih.gov/studies/index.cfm) – the flagship child and adolescent trial funded under the NIH contract mechanism. In each case, these studies begin to approach the question of which treatment is best for which child with what set of predictive characteristics (Jensen, 1999; March and Curry, 1998).

In 1983, Sir Michael Rutter opined that 'while a good deal is known about risk factors and areas amenable to prevention, less is known about how to intervene to bring about desired results' (Rutter, 1983). With a caveat or two (Clarke et al., 1995), the focus will likely remain on treating mentally ill youth rather than on primary or even secondary prevention strategies for the time being (Harrington and Clark, 1998). To move from treatment to prevention, a much more developmentally sensitive sophisticated understanding of the neurobiology of mental illness and of person and environment interactions will be necessary. While we wait for the requisite high-risk and genetic epidemiological investigations to bear fruit, the developmental perspective concerning behavioural neuroscience illustrated in the articles presented in this Special Section of *IJNP* promises to add substantially to both the nosology and rational treatment of mentally ill children and adolescents.

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