PSYCHOPHARMACOLOGY:

The Role of Pharmacotherapy in the Management of Self-Regulation Difficulties in Young Children

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Abstract
Objective: To review adjunctive pharmacotherapeutic options in the management of self-regulation difficulties in young children. **Methods:** Review of available literature and clinical experience pertaining to use of psychiatric medications in preschool aged children (under age 6). **Results:** Relatively few medications are approved for use in preschool aged children. Pharmacotherapy in this age group may include melatonin for sleep disorders, psychostimulants for Attention Deficit/Hyperactivity Disorder (ADHD), selective serotonin reuptake inhibitors (SSRI), second-generation antipsychotics, mood stabilizers and alpha-agonists. Medication efficacy and adverse effects in this age group are poorly characterized and limited by lack of age-appropriate monitoring scales and published clinical experience. **Conclusion:** As an adjunctive measure, pharmacotherapy is sometimes warranted in young children who are unable to self-regulate their physiological, emotional and behavioural responses.

Self-regulation is an interlinked phenomenon comprised of environmental influences on brain structures through neuronal, neurohormonal, and neuromodulatory processes (Fox et al., 2001). There is no standardized definition of regulation/dysregulation and its place as a methodological and conceptual construct is often debated (Cole et al. 2004).

When on a normal trajectory, self-regulation represents balanced physiological, attentional, emotional, behavioral, and cognitive processes underlying adaptive behaviors (Calkins & Fox, 2002) with interrelated impact on social functioning. Preschoolers and infants constitute a major group of referrals to pediatric and child psychiatry clinics with behavioural, emotional and social dysregulation issues (Wilens et al. 2002) and are the target population discussed in this article.

These children often present with externalizing disorders, internalizing disorders and aggressiveness (Calkins, 2000; Cicchetti, 1991; Rubin & Asendorpf, 1993). Attentional, regulation and sensory difficulties are commonly present as well, however, self-regulation difficulties are unlikely to be identified as a primary entrance complaint. Psychiatric or pediatric consultation is most often sought because there is discomfort at the parental, family, or community level. The full description of self-regulation as a concept is beyond the scope of this article, and has been reviewed elsewhere (Cole et al., 2004; Eisenberg, 2001, Eisenberg et al. 2004; Feldman, Greenbaum, & Yirmiya, 1999; Fox & Calkins, 2003; Kochanska, et al., 2000; Posner & Rothbart, 1998).

Emotional dysregulation in young children is exhibited on a spectrum of difficulties often accompanying many known childhood mental health disorders (Cole et al., 2004; Keenan, 2000). *Behavioural dysregulation* is the failure to master effortful regulation which is the ability to inhibit or activate behavior in response to the demand of the situation (Kochanska et al, 2000). *Social or interpersonal dysregulation* is also observed in young children who are unable to conform to developmental social codes (i.e. not participating in circle time, being suspended from preschool due to peer aggression).

Use of medications in preschoolers remains controversial mainly because of a paucity of evidence based data obtained from well conducted randomized controlled medication trials in this age group. Recently, The Preschool Psychopharmacology Working Group (RPWG) published recommended algorithms for medication use in preschoolers. The RPWG emphasized responsible treatment for preschoolers

and acknowledged that medication use may be sometimes necessary (Gleason et al., 2007). To add to the complexity, we know there is rapid enhancement of executive function and experience-dependent maturation of the pre-frontal cortex (Schore, 1991) but the effects of psychotropic medication on neuromodulatory and neurodevelopmental brain function in preschoolers is largely unknown.

In spite of this, off-label prescribing of psychotropic medications in this population is increasing, with a prevalence of psychotropic medication use of 2.3% in this age group in a 2001 review. With an estimated US population of 22 million children under the age of 6, this translates to approximately half a million preschoolers in the United States alone receiving psychotropic medications (Zito et al., 2007; Zito et al., 2000). This article hopes to add clinically relevant information regarding the use of medications in this relatively understudied age group.

Physiological Dysregulation

Whereas physiological regulation early on emphasizes competence in state regulation and sleep-wake cycle, later it is entwined with other domains of regulation such as attention, emotion and behavioral regulation (Sethi et al. 2000). This early dysregulation manifests in terms of sleep-wake cycle abnormalities, irritability or fussiness. Babies exposed to alcohol, nicotine, cocaine, methamphetamine or other psychotropic drugs *in utero* exemplify this dysregulation, and may not require pharmacological intervention. For example, transient jitteriness observed in babies exposed to SSRI resolves over time without pharmacotherapy (Oberlander et al, 2004).

Melatonin is helpful for sleep regulation and synchronization of the circadian rhythm in infants that do not sleep and/or remain fussy in periods of awakening. Sleep–phase onset delay and free-running circadian rhythm disorders respond better to melatonin therapy than other circadian sleep disorders.

It is recommended to start melatonin at a low dose, from 1-3 mg in toddlers and 2-4 mg in older children, and increase gradually until a satisfactory response is obtained. Vivid dreaming has been reported with melatonin but no other serious adverse effects are described (Jan & O'Donnell, 1996). Melatonin is available in capsules, sublingual, liquid and powder forms as well as sustained release tablets which may promote sleep for up to six hours or more. Duration of treatment depends upon establishing healthy sleep hygiene. Children with brain damage often require a higher dosage of melatonin. Severely neurologically disabled children may require melatonin therapy for years (Carr et al., 2007).

Behavioural and/or Attentional Dysregulation

Attentional self-regulation emerges around the end of the first year and matures toward preschool and school years. The first attention system is operational from as early as three months and consists of orienting and exploring behaviors whereas the second attention system sets in around 18 months and enhances around four years equipping the young child to partake in rule governed milieu (Ruff & Rothbart, 1996). Some children fail to achieve behavioural and attentional self-regulation as they grow up leading to disruptions in their adaptive and academic functioning in school, daycare and at home.

The rate at which preschoolers received 3 categories of medications (psychostimulants, antidepressants and/or other antipsychotic drugs) doubled between 1991 and 1995 (Zito et al., 2000). These figures are alarming considering that no antidepressants or antipsychotics are approved for children under the age of six. Additionally, not all psychostimulants are approved for young children.

Psychostimulants may be prescribed for preschoolers with behavioural disorders, though there is considerable variability in response to psychostimulants (Kratochvil et al., 2004, Wolraich, 2003). Rebound phenomena and insomnia are often responsible for premature termination of psychostimulant therapy. Rebound effects that mimic aggression appear to be more pronounced with amphetamine derivatives compared to methylphenidate. Parents and caregivers need information about the common and serious potential adverse effects of psychostimulant therapies through verbal and written counseling materials, and where possible with the use of visual aids. As shown in Table 1, not all medications used for ADHD have received approval for use in preschoolers.

Table 1. ADHD Medication Approval Status by Age (Compendium of Pharmaceutical Specialties, 2008, Physicians' Desk Reference, 2008)

Age	ADHD Medication Approval Status
Under age of three	None
Age three onwards	D,L-amphetamine (mixed amphetamine salts)*, dextroamphetamine*
Age six onwards	methylphenidate preparations (immediate release, sustained release and transdermal§ preparations), dexmethylphenidate§, lisdexamfetamine§, atomoxetine
Age 12 onwards	clonidine**
Age 18 onwards	bupropion**, desipramine**

** Medication approved by FDA but not Health Canada for ages three to six*
*** Second-line therapy, not specifically approved for treatment of ADHD*
§ Not available in Canada

Atomoxetine is a second-line ADHD treatment gaining in popularity since it is a norepinephrine reuptake inhibitor rather than a psychostimulant, and thus has minimal potential for abuse and diversion. At present, atomoxetine is not approved for use in preschoolers.

Tricyclic antidepressants (TCAs) have been used as a second line treatment for ADHD; however, they are not approved for this indication by the US Food & Drug Administration (FDA) or Health Canada. Desipramine has been implicated in at least 5 cases of sudden death in children. Therefore clinicians need to exercise caution when prescribing TCAs to young children (Riddle et al., 1991; Riddle, et al., 1993; Luby et al., 2003; Luby et al., 2004). Many clinicians do not have experience with use of TCAs, and are not comfortable prescribing these drugs to children. Despite this, TCAs may still have a minor role in treatment when associated features of treatment-resistant enuresis are present (Chertin et al. 2007).

The χ_2-agonist clonidine has been used when comorbid symptoms, aggressiveness or impulsivity complicate a behavioural pattern. Clonidine has a potential role in treating young children with post-traumatic stress disorder presenting as aggressive outbursts (Harmon & Riggs, 1996; Hazell & Stuart, 2003). An alternate χ_2-agonist guanfacine has been trialed in young children with some efficacy being demonstrated (Lee, 1997). However, this drug is not currently available in Canada.

Families who are reluctant to administer medications to young children often condone the use of non-traditional regimens of fish oil, omega-3 fatty acids (Ross et al., 2007), caffeine or gingko biloba in the treatment of their hyperactive or inattentive children. Presently, there is no evidence to support the efficacy of these non-traditional regimens in young children. A balanced discussion of the potential risks and benefits of non-traditional medications should occur in these situations.

For children entering elementary school, a careful medication protocol is necessary. There are excellent practice parameters published on the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) website (*www.caddra.ca*) regarding use of psychotropic medications in children. Readers are also alerted to recent warnings on several medications that are used in children (see *www.hc-sc.gc.ca* and *www.fda.gov/cder/index.html*).

Of all the principles emphasized in the guidelines, the most applicable to young children and most often omitted is assent and consent for treatment. Most of the time parents may be susceptible to accepting the suggestion of medication use readily, and may not pay careful attention to benefits and risks of pharmacotherapy. Another group of parents may never want to hear about the medications but they too, need to be informed of when, why, and how a specific medication treatment regimen is recommended. Clinicians should provide *'Meducation'* to children and parents and obtain informed assent/consent (Kutcher, 1997).

Attribution biases can include attitudes pertaining to acceptance and understanding of the diagnosis (e.g. ADHD), general beliefs about medication, media influences and misinformation surrounding medication use in preschoolers. These biases and a desire to take a "wait and see" approach can affect management of the child's illness. Age-specific attribution biases can also influence the decision to use

pharmacotherapy in young children. Caregivers and therapists often normalize observed activity and impulsiveness in a child based upon their perceived normative prototypes of a well functioning preschooler.

Many parents and clinicians are justifiably worried about psychostimulant use in young children due to concerns about effects on growth velocity. This controversial issue was raised again with the results of the 2004 MTA study indicating changed growth patterns in children receiving psychostimulants. A height deficit of approximately 1 cm/year was reported during the first two years of psychostimulant therapy. The beneficial effects of drug holidays on height velocity were reported as well (Klein & Mannuzza, 1988, Klein et al., 1988; Poulton & Cowell, 2003; Greenhill et al., 2003, MTA Cooperative Group, 2004). The PATS (Preschool ADHD Treatment Study) cautioned about reduction of growth (1.38 cm/year for height and 1.32 kg/year for weight) in preschoolers treated continuously with stimulant medications (Swanson et al., 2006; Abikoff et al., 2007). In the PATS study, an important clinical inference was that preschoolers with ADHD tolerate methylphenidate, but more emotional lability was noted. The effect size was smaller in preschoolers compared to responses noted in school aged children (Greenhill et al., 2003; Greenhill et al., 2006). It was also noted that presence of more than three comorbidities with ADHD predicted no treatment response to methylphenidate (Ghuman et al., 2007).

The third factor that is distinctive with preschool populations is the risk of accidental ingestion of medication. Most preschools, daycares and kindergarten classes are not able to administer medications on their premises. Self-medication even by well functioning preschoolers is never advisable. Published reports exist of children ingesting methylphenidate in an unintentional manner. Agitation, irritability, somnolence and abdominal pain were described in 21 patients who accidentally ingested methylphenidate (Poulton & Cowell, 2003; Bailey et al., 2005). It is well known that dysregulated children often live in chaotic environments. Safe storage and administration of medications prescribed for children of any age should be part of the regular psychoeducation of parents and caregivers.

Self-dysregulation with predominant impulsive aggression

Though we do not advocate their routine use, preschoolers exhibiting difficulties with self-soothing and impulsive aggression may derive short-term benefits from medications such as SSRIs. These medications have fallen into disfavour in children partly because of their capacity to produce irritability, aggression, disinhibition and suicidal ideation, and are not recommended as a first line of treatment for impulsive aggressiveness. Health Canada has not approved any SSRIs for use in children under the age of 18. However, efficacy and safety data does exist for some of the SSRIs in children, and the FDA has approved fluoxetine in children age 12 and over, sertraline in children age 7 and over, and fluvoxamine (approved only for use in obsessive-compulsive disorder) in children age 8 and over (Physicians' Desk Reference, 2008).

Despite diagnostic difficulties and emerging research, opposing views exist and the unique developmental expressions of mood disorders in very young children is still debated (Luby et al., 2003; Luby et al., 2004). There is interest from clinicians in using mood stabilizers for treatment of mood disorders in preschoolers. Some retrospective chart reviews and case reports are cited in a recent review article, but the studies are small and are not methodically vigorous enough to allow us to draw (Gleason et al., 2007). There are difficulties justifying use of medications with a serious side effect profile in young children. Lithium for example, needs careful monitoring of kidney and thyroid function, calcium-phosphorous indices and cognitive functioning (Silva et al., 1992; Silva, 2005, Wozniak, 2005).

Carbamazepine may be beneficial, but due to its side effect profile its use should only be considered in preschoolers when a co-morbid neurological condition (e.g. a seizure disorder) is suspected. Carbamazepine is available in a liquid as well as a chewable tablet and the daily dose should usually be given in three divided doses. Though a controlled-release (CR) tablet is available which may help to improve compliance, it is usually impractical for young children. During the dose titration phase; CR tablets should not be used as many children in this age group will experience difficulty swallowing the CR tablets. There can be difficulties in

attaining a therapeutic blood level with carbamazepine due to the auto-induction of cytochrome p450 liver enzymes which requires close monitoring and dose adjustment. Serum drug level monitoring is a challenge with preschoolers, who often are afraid of needles and invasive procedures.

Children may exhibit a behavioural syndrome caused by gabapentin that can add substantially to the initial aggressive and irritable state of a dysregulated child (Wolf et al., 1995). Valproate is associated with obesity and induction of polycystic ovarian syndrome in females, and toxic effects on the liver in young children. Though a significant risk of adverse effects preclude routine use in this age group, when impulsive aggression occurs as a presenting symptom of a neurological syndrome, valproate may have a role for the emotionally dysregulated child who has poor caregiver support. Young children receiving valproate require routine monitoring of liver enzymes to check for hepatotoxicity (Compendium of Pharmaceutical Specialties, 2008).

Although clonidine is useful as a modulator for intermittent explosive impulsivity and an alternative treatment for ADHD, this drug is not routinely used since extra monitoring of cardiovascular status is required due to reports of sudden death (Maloney & Schwam, 1995; Swanson et al., 1995; Daviss et al., 2008).

Emotional Dysregulation

Emotion regulation is an integral part of self regulation and is understood as a "process that can occur prior, during, or after the elicitation of emotion" (Eisenberg, 2004). Distinction of whether or not behaviour falls within developmental norms, and the strategies that a child uses to regulate mood are important.

If a child has frequent unprovoked temper tantrums lasting more than thirty minutes occurring in multiple settings (such as at preschool, parks, shopping centers, and home) and the child cannot be distracted, usual parenting strategies may be insufficient to calm the child. Child's acute stress can be helped with the use of anxiolytic medications. Lorazepam is a benzodiazepine commonly used in emergency settings. This anxiolytic has a reported half-life of 6-17 hours in children. The most frequently reported adverse effects of benzodiazepines are drowsiness, dizziness, confusion, ataxia, nausea, vomiting, stomach pain, agitation, and altered sleep patterns. In children with organic brain disorders or aggressive and impulsive tendencies, benzodiazepines can induce paradoxical disinhibition reactions which may include irritability, hostility, tantrums, aggression, insomnia, nightmares, overexcitability, hyperactivity, rage spells, hallucinations or oppositional behavior. The use of benzodiazepines in young children should be limited to emergency situations (Bezchlibnyk-Butler & Virani, 2007).

Discussion on predominant emotional dysregulation is not complete without addressing separation anxiety disorder, which is one of the most commonly presenting internalizing disorders in young children (Dieleman & Ferdinand, 2008). This disorder typically affects the self-other dysregulation axis. The child is perfectly happy if left with the preferred caregivers or in an environment the child perceives as safe. However, the interventions have to be put in place quickly due to the child's inability to individuate and perform common developmental tasks such as going to school or engaging in peer play.

Use of medication in this scenario is usually as an adjunct to ongoing behavioural therapies. Clinically, SSRIs have been used with success in helping the child and family negotiate the transition to kindergarten. However, most studies include children above age seven, thus excluding preschoolers (Clark et al., 2005).

The effectiveness of SSRIs such as fluvoxamine for treatment of anxiety disorders in children and adolescents has been demonstrated (Research Unit on Pediatric Psychopharmacology Anxiety Study Group, 2001). It is problematic to discuss, defend or rationalize use of SSRIs in preschoolers. Recent research shows that mood disorders can be identified reliably in preschoolers (Luby et al., 2002). However, there are no studies documenting efficacy of SSRIs in the treatment of mood lability in young children. Fluoxetine is the only SSRI approved by the FDA (but not by Health Canada) for the treatment of pediatric depression. When used in preschoolers, baseline laboratory measurements must include assessment of liver function and complete blood count. Unfortunately, there will always be some children who will not respond to non-pharmacological therapies. There must be extra caution and time invested in educating

parents, discussing and documenting target symptoms, providing a good network to monitor the child's symptoms, and most importantly, a plan for termination of medications.

Posttraumatic stress disorder in young children often can be misconstrued as aggressive impulsive behaviour. In such cases clonidine is used with some success in reducing rage attacks (Harmon & Riggs, 1996).

Self-Injurious Behaviour

Self-injurious behaviour exists in young children, usually as a comorbid presentation. Typical presentations of a dysregulated preschooler hurting himself include rocking, head banging, skin picking, scratching and hair pulling.

One of the important reasons why clinicians would use a medication such as risperidone is for aggression that has a compulsive quality. One good example is head banging until bleeding results, or skin picking or chewing until keloids are formed. Second-generation antipsychotics such as risperidone have a place in treating aggression (Parikh et al., 2008). Risperidone has high affinity to the serotonin type 2 ($5\text{-}HT_2$), and dopamine type 2 (D_2), and $alpha_1$ adrenergic receptors. It does not bind significantly with muscarinic receptors thus anticholinergic side effects are not experienced. If the aggressive behaviour has a compulsive quality, psychotropic medications may be needed for a longer duration.

The opioid antagonist naltrexone is indicated in extremely difficult cases where there is a serious overlay of self-injurious behaviour and a chronic disability such as autism or mental retardation (Cazzullo et al, 1999). These patients are thought to engage in self-injurious behaviours in order to stimulate endogenous opioid release. Naltrexone prevents patients from experiencing the reinforcing pleasurable effects of the opioids, and works to break the cycle of self-injurious behaviour. Long-term effects of naltrexone are unknown. Extra monitoring is suggested because of alteration in levels of cortisol, adrenocorticotropic hormone, and luteinizing hormone (Kutcher, 1997).

Acute crises with dysregulated children (emotional, behavioural and social)

In infancy, excessive crying greater than 3 hours/day for more than 3 days/week for the preceding 2 or 3 weeks is worrisome. Sleep and feeding difficulties can present together complicating management issues. Most infants stop being irritable or crying constantly by three months. Although parents often attribute excessive crying to gastroesophageal reflux and colic, there is no causal relationship established. Therefore it is unlikely that non-psychotropic medications such as simethicone, ranitidine or omeprazole may be effective in controlling the irritable and crying infant.

The use of antipsychotics may be required in children exhibiting aggressive behaviours which are unsafe and impulsive and occur without provocation. None of the antipsychotic preparations are FDA or Health Canada approved for children under the age of six. Medications are prescribed for aggressive preschoolers even though empirical support is minimal. Second-generation antipsychotics are often prescribed first, followed by stimulants and alpha agonists (Staller, 2007).

Weight gain and metabolic abnormalities with second-generation antipsychotics are disproportionately higher in children as compared to their adult counterparts receiving the same medication, and may be more pronounced with olanzapine (Correll, 2005; Fraguas et al., 2008; Findling, 2008; Klein et al., 2006).

First-generation antipsychotics such as chlorpromazine are indicated when an acute crisis has to be resolved. An average preschooler weighs 32-38 pounds (approximately 15-17 kg). The usual dose that can be given is 0.5 mg/kg/dose every four hours, by the oral, intramuscular or rectal route. Side effects range from hypotension to sedation and extrapyramidal side effects are described. Children with an acute illness are more susceptible to dystonic reactions.

Use of haloperidol may be justified in an acute crisis. However, extremely close monitoring for emergence of dystonic reactions and extrapyramidal side effects is essential. Use of intramuscular haloperidol is not studied in young children and that route should be avoided. It should be noted that all first and second generation antipsychotics can induce a potentially fatal neuroleptic malignant syndrome (NMS). Symptoms of NMS include stiffness and unexplained fever, and require immediate medical evaluation.

In emergency and child psychiatry inpatient

units, off-label use of medications poses a judgment dilemma. Clinicians have to weigh the benefits and risks of treating or not treating young children with medications. In a dysregulated child, a crisis is often reached without provocation and keeping the child safe is the utmost priority.

Ongoing Challenges and Unresolved Issues

Comorbidity is common in young children. The comorbid presentation of Autism Spectrum Disorder and Disruptive Behaviour Disorder (e.g. temper tantrums, excessive anxiety) is a common clinical situation. There are several reports of efficacy of risperidone in this population (Shea et al., 2004). Children with Down syndrome or with intellectual disability may have a difficult time controlling self-stimulatory behaviour. Verbal and behavioural approaches sometimes do not work, making the case for psychotropic use in these children. Parents sometimes note that their child seems to be doing worse during treatment with an antipsychotic medication. This perception may be based on the observed side effects of antipsychotic therapy such as extrapyramidal side effects, drooling, cognitive dulling or tardive dyskinesia, and management of identified side effects is warranted.

The off-label use of drugs such as antipsychotics and anticonvulsants is common with comorbid presentations. One medication that has a place in the treatment of aggression and self-stimulatory behaviours is carbamazepine. Drug interactions and side effects are common with antiepileptics and are often more severe in young children (Sandson et al., 2005; Sandson, 2005). This phenomenon is more frequent when concurrent medications compete for the same metabolic pathway; e.g. cytochrome p450 3A4.

Impulsive problem solving, especially in social settings remains an ongoing problem with children with self-regulation difficulties. Conversely, not all children showing social inappropriateness need pharmacological interventions. In young children, social consequences have to be seen in context. In dysregulated children, difficulties in modulating negative emotions are almost always accompanied by poor problem solving and can take the form of hitting, thrashing, destroying property or hurting siblings.

Limitations

Although there is a trend toward testing of medications in young children, such as in the PATS study (Greenhill et al., 2006), we are still limited by a lack of clinical information on pharmacotherapeutic interventions for dysregulated preschoolers. Monitoring the efficacy and effectiveness of psychotropic medications in this age group is challenging.

Clinical Implications

Self-regulation difficulties are clinically complex; these complexities are to be respected in research designs to benefit children first. Research priorities with preschoolers need reworking if we accept that even a small percentage of young children might benefit from adjunctive use of psychotropic medications. It may not be appropriate to extrapolate knowledge of psychotropic medications from studies conducted in older children and adults and apply the conclusions to this age group. When interpreting results of research conducted with preschoolers, one needs to take into account context-specific and development-specific differences between children (Greenhill et al., 2003). As with any use of off-label psychotropic medications in children, baseline investigations and monitoring are necessary.

In conclusion, the burden of living a dysregulated life should not be left to young children and their distressed families. Regulation difficulties in preschoolers and young children have to be resolved through a multifaceted responsible approach. Of these approaches, psychopharmacological intervention is an important avenue that should not be ignored even if it is only helpful to a select subset of this population.

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