European Psychiatry 62 (2019) 58–59

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Atypical antipsychotics for Attention-Deficit/Hyperactivity disorder- science, art, or fad?

Use of atypical antipsychotics (AAPs) for attention-deficit/hyperactivity disorder (ADHD) is currently rife and trend of use is on the rise. It is largely off-label driven. Here, we touch on the topic highlighting both merits and demerits of this approach.

Pharmacotherapy remains the cornerstone of ADHD treatment. [1] ADHD 'simplex' is a rare clinical occurrence. Co-morbidity is the rule rather than the exception in circa 80% of cases [2]. This heterogeneity and complexity of ADHD presentations has been reflected on treatment regimens and polypharmacy is on the rise. It has been demonstrated that 20–35% of subjects in clinical trials show inadequate response to stimulants that could be attributed in part to dose-limiting side effects of medications or disorder severity or complexity [3]. Noteworthy mentioning is the rampant use of add-on atypical antipsychotics (AAPs) for ADHD intricacies; whether part of syndrome, comorbidities or stimulant-induced [4] AAPs are commonly deployed to address behavioural facets (e.g. conduct disorder with risperidone having the best-evidence). AAPs can help offset insomnia through H1 blockade, 5HT2A antagonism, α1 adrenolytic actions and possible 5HT7 antagonism. Also, AAPs can mitigate anxiety through 5HT1A agonism, serotonin or serotonin-norepinephrine reuptake inhibition actions of some AAPs. Moreover, AAPs can rectify stimulant anorexia through H1 antagonism and 5HT2c antagonism. For comorbid tics, AAPs, via DA blockade, might be an option. Some clinicians (including this author) use antipsychotics as a scaffold to base stimulant treatment in order to safeguard against evening rebound symptoms when stimulants wear off and meanwhile ensure tighter behavioural control for severe behavioural presentations [5]. Certain populations are likely to be prescribed AAPs from the outset including preschool ADHD, hyperkinetic autism spectrum disorder (ASD), epileptics or those with intellectual disability [6]. Even an RCT could not demonstrate a significant difference between risperidone and methylphenidate (MPH) for preschool ADHD on the Parent ADHD Rating Scale and Parent Conners Rating Scale scores over 6-week duration [7]. Nonetheless, review of literature reveals limited randomized controlled trial (RCT) data for combination psychostimulant and antipsychotic use. Although several guidelines recommend combination therapy with psychostimulants and antipsychotics to treat comorbid aggression and ADHD, it is suggested only as a third-line option following sequential monotherapy trials of psychostimulants and behavioural interventions. Despite the established efficacy of psychostimulant and antipsychotic monotherapy, the evidence for the efficacy of combination therapy is limited and not based on strong data [8]. This notion is not new, however. This can be gleaned from the old FDA label of haloperidol reading an indication for hyperactivity and disruptive behaviours in children 3 years of age and older [9]. This might sounds somewhat counterproductive, ab initio, mechanistically to give an antipsychotic with potent D2 blockade in ADHD which is basically a hypodopaminergic state and hence the use of stimulants to boost dopamine (DA) drive in the prefrontal cortex (PFC). This has been largely refuted by 2 studies. In one study by Aman et al. [10] risperidone had no detrimental effects on cognitive performance in ASD population, twenty-nine boys and 9 girls with autism and severe behavioral disturbance and a mental age older than 18 months completed the cognitive part of the study. No decline in performance occurred with risperidone. Performance on a cancellation task (number of correct detections) and a verbal learning task (word recognition) was better on risperidone than on placebo (without correction for multiplicity). Equivocal improvement also occurred on a spatial memory task. There were no significant differences between treatment conditions on the Purdue Pegboard (hand-eye coordination) task or the Analog Classroom Task (timed math test).

The other study by Gunther et al. [11] risperidone had no negative impact on cognitive functions. In this study, children with ADHD and disruptive behaviour disorders (DBD), aged 8–15 years, were treated with risperidone (mean daily dose: 1.5 mg; n = 23) and examined with three attentional paradigms before and after a 4-week treatment period. Age- and IQ-matched normal controls (n = 23) were also tested without medication on the same two occasions. No influence of the medication could be detected for any neuropsychological variable, neither as a positive enhancement nor as adverse side effects. However, clinical symptoms of ADHD and DBD assessed on the IOWA Conners Scale significantly improved after the 4-week treatment period. Divergent behavioral and cognitive effects of risperidone on ADHD symptoms were observed, with a significant reduction in behavioral symptoms, whereas no positive treatment effects were found on laboratory tasks of impulsivity. Thus, the cognitive effects of risperidone seem to differ from the cognitive effects of stimulant treatments in children with ADHD + DBD. However, no negative impact of risperidone was observed on attentional functions either, i.e., there was no slowing of cognitive speed.

http://dx.doi.org/10.1016/j.eurpsy.2019.08.013

Table 1
'Complex DA Model' in medicated and non-medicated ADHD.

	Neurobiological Underpinnings And Mechanisms
ADHD	↓tonic dopamine (DA) & ↑DA bursts
Stimulants	Presynaptic action; ↑tonic DA; ↓DA bursts; postsynaptic downregulation
Antipsychotics	Postsynaptic action; ↑tonic DA; ↓DA bursts; postsynaptic upregulation
Stimulants + Antipsychotics	↑tonic DA; ↓DA bursts (pre & postsynaptic actions); no net change in postsynaptic regulation

Yanofski [12] has proposed an interesting 'complex DA model' in an attempt to explain these apparently counter-acting mechanisms. This is summarized in Table 1 Moreover; use of certain AAPs might enhance cognition. Aripiprazole by partial D2 agonism and 5H1A agonistic activity can be pro-cognitive. Also, quetiapine by virtue of 5HT1A agonim, 5HT6/7 antagonism, norepinephrin transporter inhibition (via its metabolite norquetiapine), 5HT2c antagonism (which translates pharmacologically into norepinephrine-dopamine disinhibition in the PFC) possesses pro-cognitive actions.

The main concern with these 'heroic combos', apart from costs, is the drastic metabolic syndrome, albeit we can counter-argue that, it might be tempered by co-administered stimulant therapy, this population is at a heightened risk by virtue of age [13]. Furthermore, the association of ADHD to obesity has been well demonstrated [14].

Also, a personal history and a maternal history of autoimmune diseases, especially type 1 diabetes, were associated with an increased risk of ADHD [15]. Recently, a nationwide prospective longitudinal study from Taiwan recently revealed adolescents with ADHD are at a higher risk to develop type 2 DM with hazards ratio of 2.83 and treatment with atypical antipsychotics increased the risk further [16]. To muddle it further, Ray et al. [17] has demonstrated that children aged 6–24 years receiving antipsychotics with chlorpromazine equivalent doses of more than 50 mg were at heightened mortality 3.5 times than control.

Prescribers of these combinations should be vigilant of possible emergent dyskinesias and such case reports abound in literature [18].

Quo Vadis? It behoves clinicians, then, to deploy a well-keeled approach when co-prescribing stimulants and AAPs manipulating merits and demerits of this 'combo' on case-to-case basis on the way to define its real place in the niche of ADHD psychopharmacotherapy.

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Received 2 August 2019

Available online 19 September 2019