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In this issue:

- A novel digital intervention for actively reducing severity of paediatric ADHD
- Subcortical brain volume, regional cortical thickness and cortical surface area across disorders
- Relationship between executive function and ADHD improvement with lisdexamphetamine
- The patient perspective: unmet treatment needs in adults with ADHD
- Effect of continuing and discontinuing medications on quality of life
- Efficacy and safety of guanfacine extended-release in the treatment of ADHD in adults
- Types of adult ADHD: a replication analysis
- Methylphenidate and mortality in children with ADHD
- Longitudinal trajectories of sustained attention development in ADHD
- Do parents' ADHD symptoms affect treatment for their children

Abbreviations used in this issue:

ADHD = attention-deficit/hyperactivity disorder; **ADHD-RS-AP-TS** = ADHD-Rating Scale with Adult Prompts total score; **AHR** = adjusted hazard ratio; **API** = Attention Performance Index; **ASD** = autism spectrum disorder; **AU** = augmenters; **BPT** = behavioral parent training; **BRIEF-A** = Behavior Rating Inventory of Executive Function–Adult Version; **CGI-S** = Clinical Global Impressions–Severity of Illness scale; **DSM-5** = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; **ED** = emotional dysregulation; **EF**=executive function; **ET** = early termination; **GEC T-score** = Global Executive Composite T-score; **GXR** = guanfacine extended-release; **ICD-10** = International Classification of Diseases; **LA** = long acting; **MPH** = methylphenidate; **NHIRD** = National Health Insurance Research Database; **OCD** = obsessive-compulsive disorder; **SA** = short acting; **SART** = Sustained Attention to Response Task; **SDRT** = standard deviation of response time; **SMD** = standardised mean difference; **TOVA** = Test of Variables of Attention; **WRAADDS** = Wender-Reimherr Adult Attention Deficit Disorder Scale.

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Welcome to the second issue of ADHD Research Review.

In this issue, a novel digital intervention improved inattention in paediatric ADHD patients, subtle structural brain differences among ADHD, ASD, and OCD were identified, both ADHD and executive function deficits improved following treatment with lisdexamphetamine, and unmet treatment needs in adults with ADHD, especially relating to the duration of effect, are identified. A Japanese meta-analysis investigated the effect of continuing and discontinuing medications on quality of life in ADHD patients, a placebo-controlled study of guanfacine extended-release in adults with ADHD confirmed its efficacy without any major safety concerns, and a Taiwanese cohort study in children with ADHD found that methylphenidate was associated with lower mortality vs the comparison group.

We hope you find these and the other selected studies interesting, and we welcome your feedback.

Kind Regards,

Dr Roger Paterson

roger.paterson@researchreview.com.au

A novel digital intervention for actively reducing severity of paediatric ADHD

Authors: Kollins SH et al.

Summary: This randomised, double-blind, parallel-group trial in ADHD patients (n=348; 8-12 years) not treated with disorder-related medications investigated a digital therapeutic (AKL-T01) designed to target attention and cognitive control through a video game-like interface. Patients from 20 research institutions in the US were randomised to AKL-T01 or a digital control intervention for at-home play for 25 minutes/day, 5 days/week for 4 weeks to establish whether AKL-T01 improved attentional performance. The primary outcome was mean change from pre- to post-intervention in Test of Variables of Attention (TOVA) Attention Performance Index (API). The mean (SD) change from baseline in TOVA API was 0·93 (3·15) in the AKL-T01 group (n=182) and 0·03 (3·16) in the control group (n=168). No serious adverse events or discontinuations were reported with frustration (3%) and headache (2%) reported as treatment-related side effects. AKL-T01 may be used to improve objectively measured inattention in paediatric ADHD patients with minimal adverse events, however further research is needed.

Comment: We live in a digital age and therefore it is no surprise to see more and more digital therapeutics being developed. ADHD is at its core an attentional disorder which encourages digital therapies that can sustain attention and perhaps increase it. This study warrants respect from its research base and journal status. The research group received so-called AKL-T01 digital therapy (they might have to work on the name for marketing!) and found that this instructional video game played on most days for 4 weeks was helpful with no major side effects. Many more of these are coming – watch this space. How they stack up in terms of generalisability and persistence of efficacy remains to be seen.

Reference: JAMA Netw Open 2020;3(3):e201417.
Abstract

Subcortical brain volume, regional cortical thickness and cortical surface area across disorders

Authors: Boedhoe PSW et al.

Summary: As ADHD, ASD and OCD often co-occur, the authors compared the three disorders using T_1-weighted whole-brain MRI data from patients with ADHD (n=2,271), ASD (n=1,777) and OCD (n=2,323) with healthy controls (n=5,827). Data from 151 global cohorts from the ENIGMA consortium were analysed. Subcortical volume, cortical thickness, and cortical surface area differences were assessed with separate analyses for children, adolescents, and adults. There were no shared differences among the three disorders, and shared differences between any two disorders did not survive correction for multiple comparisons. In children, patients with ADHD had smaller hippocampal volumes compared with those with OCD, possibly influenced by IQ. In children and adolescents with ADHD, intracranial volume was smaller compared with controls and those with OCD or ASD. When compared with adult controls and other clinical groups, adults with ASD had thicker frontal cortices. There were no OCD-specific differences across age groups. The findings demonstrated subtle structural brain differences among ADHD, ASD, and OCD across age groups supporting previous research findings.

Comment: The search goes on for disease-specific structural brain changes, and in this paper, there is further evidence that ADHD, ASD and OCD have recognisable differences. Traditionally, ADHD cortical changes have been considered to be signs of immaturity as they normalise over time, and possibly more so with treatment which is encouraging.

Reference: Am J Psychiatry 2020;177:834-843.
Abstract

Relationships between executive function improvement and ADHD symptom improvement with lisdexamfetamine dimesylate in adults with ADHD and executive function deficits

Authors: Brown TE et al.

Summary: In this post-hoc analysis, data from a 10-week double-blind, placebo-controlled study of adults with ADHD and executive function (EF) deficits treated with lisdexamfetamine (30–70 mg) or placebo were analysed. Change from baseline at week 10/early termination (ET) in self-report Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A) Global Executive Composite (GEC) T-score and ADHD-Rating Scale with Adult Prompts total score (ADHD-RS-AP-TS) were assessed as efficacy endpoints. The relationships between ADHD symptoms and EF changes were measured using recursive path analyses. Mediation proportions were 0.62 for self-report BRIEF-A GEC T-score change from baseline at week 10/ET on ADHD-RS-AP-TS and 0.93 for ADHD-RS-AP-TS change from baseline at week 10/ET on self-report BRIEF-A GEC T-score. ADHD symptom and EF deficit improvements following lisdexamfetamine were interdependent. Measures such as the BRIEF-A to assess stimulant effects on a wide range of EF deficits associated with ADHD are an advantage as it captures information not reported using the ADHD-RS-AP alone.

Comment: The relationship between EF and ADHD has long been a source of debate. There is no doubt that EF issues are often a problem in ADHD, but are they primary or secondary? This study looks further at the relationship and found that both ADHD and EF deficit improved following treatment with lisdexamphetamine, but that they improved independently, and that future research should use scales which assess both ADHD scores and executive function scores (e.g. as measured by a popular EF scale, BRIEF-A).

Reference: Prim Care Companion CNS Disord 2020;22:19m02559
Abstract

The patient perspective: unmet treatment needs in adults with ADHD

Authors: Brown TE et al.

Summary: Brown and co-workers assessed the impairments in daily life and unmet treatment needs in adults with ADHD treated with medication (n=616) vs adults without ADHD (n=200). This cross-sectional online survey included adults with ADHD treated with prescription medicine for ≥ 6 months and adults without ADHD. ADHD participants were stratified based on their current medication: long acting (LA) once daily (n=201), short acting (SA) ≤ 2 times/day (n=166), and augmenters (AU; LA > once/day, SA > 2 times/day, or LA plus SA; n=249). Despite treatment, patients with ADHD reported substantial impairments and challenges in everyday life (at home, at school/work and social/relationships) especially in the afternoon and evening. Negative effects, including schoolwork, homework, work responsibilities, household responsibilities, emotional responses, mood, and relationships resulted when medication was wearing off. Participants reported various unmet treatment needs, especially relating to the duration of effect. Adult treatment regimens should be optimised to meet the patient's needs throughout the day.

Comment: Psychologist Thomas Brown has a long and distinguished ADHD research career and he has some important things to say about medicated adult ADHD patients, and what are some of the treatment shortcomings. It seems they experience many impairments and challenges in aspects of their daily life, especially treatment wearing off each day, and as we know, adults often have a number of duties which persist long into the evening/night, both home duties and study/work tasks. Longer-acting formulations have been a boon in this regard.

Reference: Prim Care Companion CNS Disord 2019;21:18m02397
Abstract

Effect of continuing and discontinuing medications on quality of life after symptomatic remission in ADHD

Authors: Tsujii N et al.

Summary: This systematic review/meta-analysis compared the effect of continuing and discontinuing medications on quality of life in ADHD patients. Five studies including 1,463 patients (children and adolescents n=894; adults n=569) measured quality of life and were included in the meta-analysis. Treatment discontinuation significantly worsened quality of life scores vs continuing medications (standardised mean difference [SMD] = 0.19; 95% CI 0.08 to 0.3). A small but statistically significant decrease in quality of life was reported in children and adolescents (SMD = 0.21; 95% CI 0.06 to 0.36) but not in adults with ADHD (SMD = 0.02; 95% CI –0.46 to 0.50). Quality of life should be considered when planning individualised ADHD treatment.

Comment: Interesting work coming from Japan on an important topic – what happens to people when ADHD medication is ceased? Well, unsurprisingly, many did not do so well but here's the thing – this is only really seen in children and adolescents, not in adults, which may be explained by what clinicians see regularly – adult patients "mature" out of their ADHD and do not seem to need medication anymore, with about a 50% persistence rate of ADHD from youth to adults. The question remains – do they really grow out of ADHD or do they just learn to manage it better without medication (e.g. have less high academic demands and settle into a more routine working life?).

Reference: J Clin Psychiatry 2020;81:19r13015
Abstract

Efficacy and safety of guanfacine extended-release in the treatment of ADHD in adults

Authors: Iwanami A et al.

Summary: The objective of this phase 3, double-blind, placebo-controlled study was to assess the efficacy and safety of guanfacine extended-release (GXR) in Japanese adults with ADHD. Patients received GXR (n = 101) titrated from 2 mg/d to 4–6 mg/d (dose-optimization; 5 weeks), followed by 4–6 mg/d (dose-maintenance; 5 weeks), then reduced to 2 mg/d (2 weeks), or placebo (n = 100). The primary study endpoint was change from baseline in ADHD-RS-AP-TS (Japanese version) at week 10. There was a statistically significantly greater improvement in ADHD-RS-AP-TS reduction with GXR vs placebo (least squares mean ± SE: GXR vs placebo, –11.55 ± 1.10 vs –7.27 ± 1.07; P = 0.0005; effect size 0.52). There were also significantly greater improvements in the GXR group for inattention (P = 0.0032) and hyperactivity-impulsivity (P = 0.0021) subscale scores vs placebo. More patients treated with GXR reported adverse events (81.2% vs 62.0%) and discontinued treatment (19.8% vs 3.0%) compared with placebo. Most frequently reported adverse events were somnolence, thirst, blood pressure decrease, nasopharyngitis, postural dizziness, and constipation. GXR improved ADHD symptoms without any major safety concerns in this Japanese cohort.

Comment: Another Japanese study which is long overdue – guanfacine has been shown to be very effective in children and adolescents, but not researched much in adults. This study confirms what has been shown in the younger age groups, notably that guanfacine improves ADHD symptoms without any major safety concerns. It is not yet TGA approved for adults in Australia but curiously it is PBS subsidised if ADHD was diagnosed under the age of 18 and treatment continues into adulthood.

Reference: J Clin Psychiatry 2020;81:19m12979
Abstract

Types of adult ADHD: a replication analysis

Authors: Reimherr FWA et al.

Summary: Emotional symptoms of ADHD are not reflected in the DSM-5 or ICD-10 criteria, however the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) assesses these symptoms as well as inattention, hyperactivity, and impulsivity. Based on this scale, adult ADHD patients were divided into 2 subtypes: ADHD inattentive presentation and ADHD emotional dysregulation presentation. For this replication analysis, eight double-blind adult ADHD clinical trials (n=1,490) which used the WRAADDS assessment, a second alternative ADHD measure and the Clinical Global Impressions–Severity of Illness scale (CGI-S) were selected. ADHD presentations and treatment response were compared using confirmatory factor analyses. The original factor structure fit poorly with the new data, but an alternative 2-factor solution fit both the original and the new subjects. The inattention factor defined patients with ADHD inattentive presentation (n = 774). ADHD emotional dysregulation presentation (n = 620) was defined by additional elevation of the emotional dysregulation factor. Across the eight included studies, the proportion of ADHD emotional dysregulation presentation ranged from 25% to 73%. The emotional dysregulation presentation was more severe when measured with the CGI-S (P < 0.001) and demonstrated more childhood manifestations of ADHD when measured with the Wender Utah Rating Scale (P < 0.001). This analysis supports the validity of two adult ADHD presentations based on levels of emotional dysregulation and offers a more clinically relevant approach to diagnosis compared with the DSM system.

Comment: From many quarters (this time from Utah), calls are coming loud and clear to highlight emotional dysregulation (ED) in ADHD. This time, the approach is to dispense with the hyperactive/impulsive subtype and continue just with an ED subtype, still retaining the inattentive subtype. This has some appeal but the problem with ED is that it is not a core distinguishing feature of ADHD as it is often seen in other psychiatric disorders, and including ED will lead to even more overlap and ill-defined ADHD boundaries. Nevertheless, ED impacts significantly on quality of life and is a clinical feature of ADHD worth addressing.

Reference: J Clin Psychiatry 2020;81:19m13077
Abstract

Methylphenidate and mortality in children with ADHD

Authors: Chen VC et al.

Summary: This population-based cohort study investigated the association between methylphenidate (MPH) use and mortality. Data from Taiwan's National Health Insurance Research Database (NHIRD) were analysed. Children and adolescents (n=68 096) with ADHD and prescribed MPH were compared with matched controls (n=68 096). Patients were followed to death, migration, withdrawal from the NHI or the end of the study period. Prescriptions for MPH were measured annually during the study and the association between MPH use and mortality was analysed using a repeated-measures time-dependent Cox regression model. Outcome measures included all-cause, unnatural-cause (including suicide, accident and homicide) and natural-cause mortality. Lower unadjusted all-cause, natural-, unnatural- and accident-cause mortality were demonstrated in the MPH vs the comparison group. MPH use was associated with a significantly lower all-cause mortality (adjusted hazard rate [AHR] = 0.81, 95% CI 0.67–0.98, P = 0.027) after controlling for potential confounders. Furthermore, delayed use of MPH was associated with higher mortality (AHR = 1.05, 95% CI 1.01–1.09) and longer MPH use was associated with lower mortality (AHR = 0.83, 95% CI 0.70–0.98).

Comment: This headline-grabbing study from Taiwan raises alarm initially and then quietude. Alarm initially as critics of ADHD medications are quick to point out any side effects, and increased mortality which would certainly be a side effect hard to ignore. Fortunately, the opposite is the case, and this conclusion is based on a huge national cohort study. They did their best not to exclude potential confounders and the two conclusions are very important – do not delay the use of methylphenidate and be very careful about discontinuing it.

Reference: Br J Psychiatry 2020 Jul 14;1-9. doi: 10.1192/bjp.2020.129
Abstract

Longitudinal trajectories of sustained attention development in children and adolescents with ADHD

Authors: Thomson P et al.

Summary: In this study the Sustained Attention to Response Task (SART) was administered to 120 children and 123 controls (aged 9–14) on three occasions to measure changes in sustained attention ability and to establish whether longitudinal trajectories of attention development differ between persistent ADHD, remitted ADHD and control groups. Trajectories of sustained attention development, indicated by changes in SART performance (standard deviation of response time [SDRT], omission errors, and ex-Gaussian parameters sigma and tau), were examined. There was a significant main effect of age for all measures. As children aged, response time variability and number of omission errors improved linearly. Compared with controls, children with ADHD had significantly greater SDRT, tau and omission errors across waves. No significant group differences in sigma were demonstrated which indicates that the greater overall response time variability (SDRT) in ADHD patients was likely driven by more intermittent long responses (larger tau). Children with persistent ADHD or ADHD in remission demonstrated similar trajectories of sustained attention performance. Comparable longitudinal trajectories of sustained attention development were observed between ADHD and controls. ADHD patients had a performance deficit equivalent to controls 1–3 years younger. Continued clinical support for children in ADHD remission is needed.

Comment: An elegant Melbourne study which wonders about what happens to attention in children over time, particularly ADHD children. They confirmed the obvious – in general, children's attention improves over time, but they teased apart the data in ADHD children and found something particularly important: ADHD children were even more significantly delayed in attention development compared with controls, and this was true of both persisting and remitted ADHD cases. The remitted group is particularly important – are they really remitted? Should there be some ongoing, low-level clinical review to check on those cases who are not truly remitted and have ongoing difficulties?

Reference: J Abnorm Child Psychol 2020 Sep 5. doi: 10.1007/s10802-020-00698-5
Abstract

Do parents' ADHD symptoms affect treatment for their children?

Authors: Friedman LM et al.

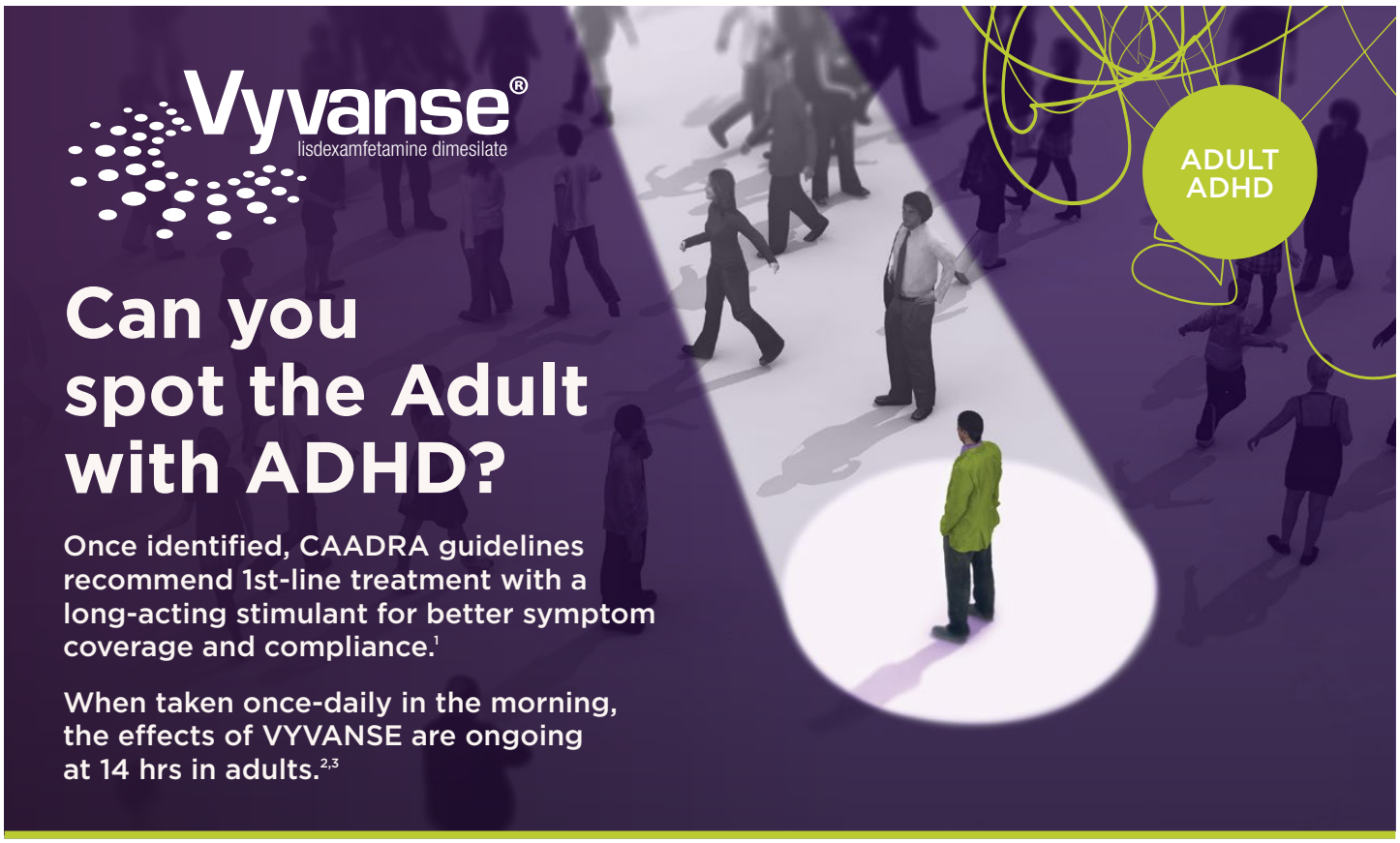
Summary: Intergenerational ADHD is a significant risk factor for poor outcomes following behavioral parent training (BPT) programs and ADHD symptoms in parents is a barrier to effective engagement with BPT treatment. This study examined the effect of parental ADHD symptoms on BPT treatment engagement for ADHD children with predominantly inattentive presentation (n = 148, ages 7–11). The following parent- and clinician-rated treatment engagement domains were examined: between-session skill adherence, in-session participation, perceived skill understanding, treatment-engagement attitudes, and session attendance. The only treatment engagement domain related significantly to parental ADHD symptoms was parent- and clinician-rated between-session adherence. After accounting for symptoms of parental anxiety and depression, child ADHD symptom severity, and various sociodemographic factors, this finding remained. Targeting parental ADHD symptoms in the context of parenting interventions may be promising to improve adherence and treatment outcomes for BPT interventions.

Comment: ADHD is strongly heritable, that we know. Many is the time that clinicians move from a focus on their child/youth patient, to pose delicately the issue of coexisting parental ADHD (in one or both parents). This becomes a real issue because often parent training is suggested and unless underlying ADHD is treated, this parent training may well be less than optimal. This finding is now well known, but reinforced by this study, and another salient reminder to clinicians that psychotherapy, of all types, is best undertaken once ADHD is being treated.

Reference: J Abnorm Child Psychol 2020;48:1425-1437
Abstract

Independent commentary by Dr Roger Paterson (FRCPsych, FRANZCP, Cert Child Adolesc Psych)

Dr Roger Paterson is a psychiatrist in central Perth specialising in adolescents and adults with ADHD. He graduated in medicine from the University of WA, and subsequently trained in child and adult psychiatry in London and Perth. Roger worked in both the public and private sectors in general child, adolescent and adult psychiatry from 1989, moving to full-time private practice in 1996. In 1999, he led a group which published the 1st ever trial of dexamphetamine usage in adult ADHD. In July 2017 he joined the inaugural board of the Australian ADHD Professionals Association and remains an active member. He also manages binge eating disorders, particularly in the field of pharmacotherapy.



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