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Research Article

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The Latest Scientific Advancements in the Multimodal Treatment of ADHD

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Abstract

Attention-deficit hyperactivity disorder (ADHD/ADD) is a neurobehavioral disorder of childhood onset characterized by severe, developmentally inappropriate motor hyperactivity, inattention, and impulsiveness that result in impairment in more than one setting. It affects the home, school, and community life of 39% of school-going children worldwide. There is increasing recognition that ADHD symptoms and clinically defined disorder can persist into adult life and are associated with later drug and alcohol misuse and social and work difficulties. Added to that is the extreme variability of the disorder over time, within the same individual, between individuals, and across different circumstances. Treatment with stimulants and nonstimulants has proven effective in different subgroups, with the effectiveness of specific agents most likely related to the primary neurotransmitter involved. However, stimulants with a short duration of action have been problematic for some patients. Parent training and cognitive behavioral therapies represent the most widely adjunct psychosocial interventions to pharmacotherapy.

Keywords: Adhd, Amphetamine, Neurofeedback, Cognitive Training, Cbt, Substance Abuse, Attention, Non-Dopaminergic Medication, Cardiovascular Effects, Neurological Effects

1. Discussion

1.1. Assessment

Attention-deficit/hyperactivity disorder (ADHD) assessment involves the integration of information from different sources and an appropriate clinical decision-making process able to resolve conflicting observations and information. The full assessment includes information collected by validated instruments documenting present problems, health and developmental history, comorbid psychiatric conditions, and global functioning; instruments and procedures include questionnaires, interviews, and, when appropriate, direct observation and neuro-psychological testing. Assessment of cardiac risk factors needs to be recorded at assessment before prescribing medications and Routinely thereafter. At the end of the assessment process, the clinician will determine a principal and differential diagnosis and the presence of any comorbidity, and

will develop a formulation that places these diagnoses in context. ADHD treatment guidelines and

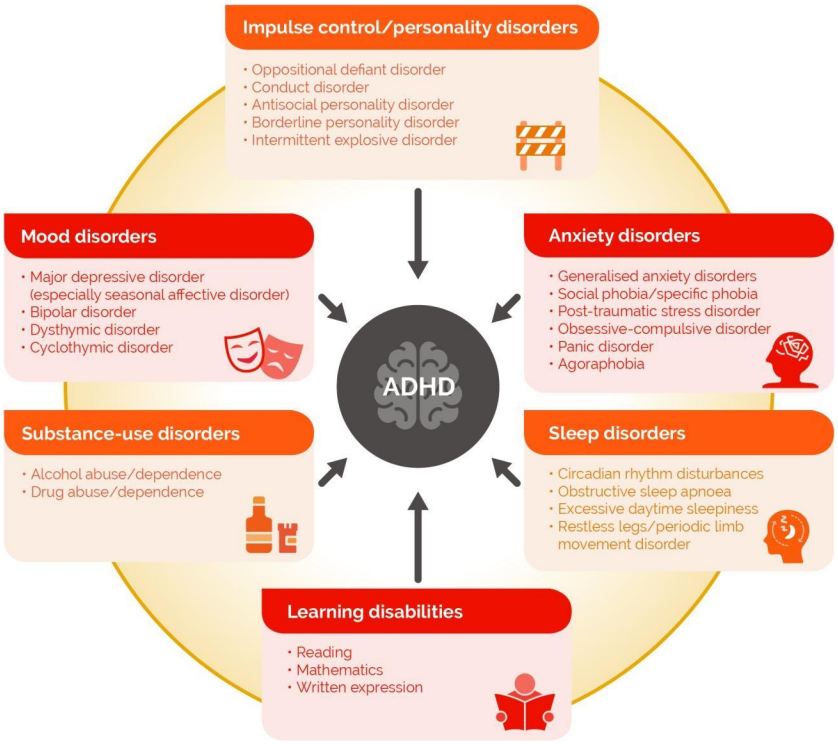

Figure 1: Comorbid Psychiatric Conditions With ADHD

algorithms have been developed in Europe [1-4] and North America [5-7], proposing evidence-based approaches for ADHD assessment and management. Model templates for planning services for ADHD assessment and intervention, such as the Dundee ADHD Clinical Care Pathway (DACCP) [8], have also been tested and are currently used in many countries. It includes specific stages for: (1) referral and pre-assessment; (2) assessment, diagnosis, and treatment planning. (3) initiating treatment, and (4) monitoring and continuing care.

1.2. Clinical Management

Treatment for ADHD is based on a multimodal approach combining Behavioural and pharmacological treatment [2,9]. European guidelines highly recommend a stepwise approach, with psychobehavioural interventions as first-line treatments, especially for pre-school children and subjects affected by a mild form of the disorder. American guidelines do not preclude pharmacotherapy as a first therapeutic approach, even in the youngest and mildest cases. If pharmacological treatment is prescribed first line, it should be combined with Behavioural interventions in any case. However, it is Largely accepted that pharmacological treatment for ADHD is highly effective, either alone or in combination with Behavioural interventions, that it has greater benefits than Behavioural intervention alone, and that outcomes are much improved when a structured approach to medication management is adopted [10]. There is not a unique strategy for management; individual circumstances, comorbidities, and medical history have to be considered as an integral part of the treatment plan; after appropriate information, parents' and patients preference should always be taken into account. When concomitant medical or psychiatric conditions such as conduct disorders, specific learning disorder, and social difficulties are present, psychosocial, psychoeducational, and environmental interventions centred on the family and school are often required. The main objectives of any comprehensive treatment are:

✓ To improve core ADHD symptoms.
✓ To improve interpersonal relationships with parents, siblings, teachers, and peers.
✓ To decrease disruptive behaviour.
✓ To improve school learning abilities.
✓ To increase personal autonomy and self-esteem.
✓ To improve social acceptability of the disorders and the quality of life of children/adolescents suffering from the disorder [11].

2. Non-Pharmacological Interventions

The most common non-pharmacological treatments are Behavioural interventions both for children and careers [that is, parent training (PT), educator/teacher training, cognitive Behavioural therapy (CBT), support groups, and social skills training], cognitive training, neurofeedback, The objective is to improve global functioning and reduce ADHD symptoms.

3. Parent Training

PT programmers are parents psychoeducational interventions providing parents with information about ADHD in order to better manage their children's, groups of parents and covers positive reinforcement skills, reward systems, the use of 'time out, liaison with teachers, and planning ahead to anticipate problems. According to recent studies, PT has positive effects on the behaviour of ADHD children by increasing parents' behaviour management skills, as well as reducing stress and improving parents sense of efficacy [12].

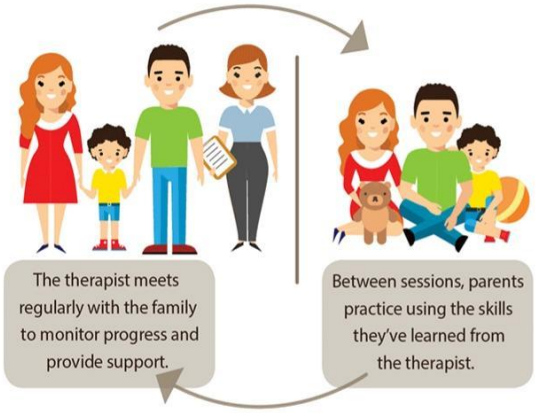

Figure 2: Parents Training Psychoeducational

4. Cognitive Behavioural Therapy

CBT is a structured psychotherapeutic approach to help subjects in recognizing their dysfunctional patterns of thought and behaviour. It aims to help subjects to learn new skills and strategies to achieve their objectives, improve self-esteem, and deal with their emotions and social difficulties. Objective evidence for the efficacy of psychosocial interventions is problematic. A recent meta-analysis by the European ADHD Guideline Group (EAGG) showed good effect sizes when outcome measures were based on ADHD assessments by raters closest to the therapeutic setting. There was an overall standardized mean difference (SMD) of 0.40 (95% CI 0.20, 0.60). However, when only ratings by assessors blind to treatment allocation were considered, treatment effects almost disappeared (SMD 0.02, 95% CI -0.30, 0.34) [13]. In contrast with the lack of sufficient evidence on ADHD core symptoms, a more recent meta-analysis showed a significant positive effect of Behavioural interventions on parenting skills and con-duct problems in ADHD children [14,15].

5. Cognitive Training

Cognitive training for ADHD involves computerized exercises that target executive functions like attention, working memory, and inhibition to improve daily functioning and academic performance. In recent years, also cognitive training aimed at targeting specific deficits (for example, attention, working memory, inhibitory con-effects of cognitive training on ADHD, as addressed in a recent time) has been investigated as potential ADHD treatment [16]. The meta-analysis performed by the same EAGG, were significant when calculated using unblinded ratings (SMD 0.64, 95% CI 0.33-0.95) but, as reported for psychoeducational interventions, became statistically non-significant (SMD 0.24, 95% CI 0.24-0.72) when measures generated by probably blinded observers were used [17]. A more recent meta-analysis, including a larger number of trials, showed a more reliable estimate of the effects of cognitive training on specific functions (working memory, sustained attention, and inhibition); when measured by blinded raters, cognitive training mainly improved working memory, with limited effects on ADHD core symptoms [17].

6. Neurofeedback

Neurofeedback is a promising non-pharmacological treatment for managing ADHD symptoms. By training individuals to modulate specific brain wave patterns associated with attention, impulsivity, and hyperactivity, neurofeedback can help improve self-regulation and reduce ADHD symptoms. The results of a recent meta-analysis on 13 controller trials did not show neurofeedback to be an effective treatment for ADHD when evaluated by probably blinded raters [18]. A recent study in adults confirmed these results, although some promising preliminary results have been reported with innovate techniques [19-21]. Behavioural interventions have also been provided as use treatments for managing comorbid disorders in ADHD, Recently, a multicentre RCT conducted in 159 adolescents, short-term cognitive behaviour Therapies (one including skills teaching, while the other was solution-focused), showed significant improvements in comorbid depression, anxiety, and disruptive disorder symptoms with both approaches [22]. Weaker evidence is available for the efficacy of Behavioural sleep interventions in children with ADHD, although about 70% of ADHD subjects display mild to severe sleep problems. Behavioural treatments for insomnia are clearly effective in children in general and ADHD should be considered not only a day-time disorder, but also better as a 24-hour ongoing process including sleep

difficulties. Given the well-known consequences of poor sleep on memory and cognition, Behavioural approaches to improve sleep may represent an important resource needing more specific research [23,24]. Some clinicians already recommend initiating Behavioural treatment for poor sleep early in management, since it is a non-contentious symptom, carrying none of the stigma of a psychiatric a gnosis.

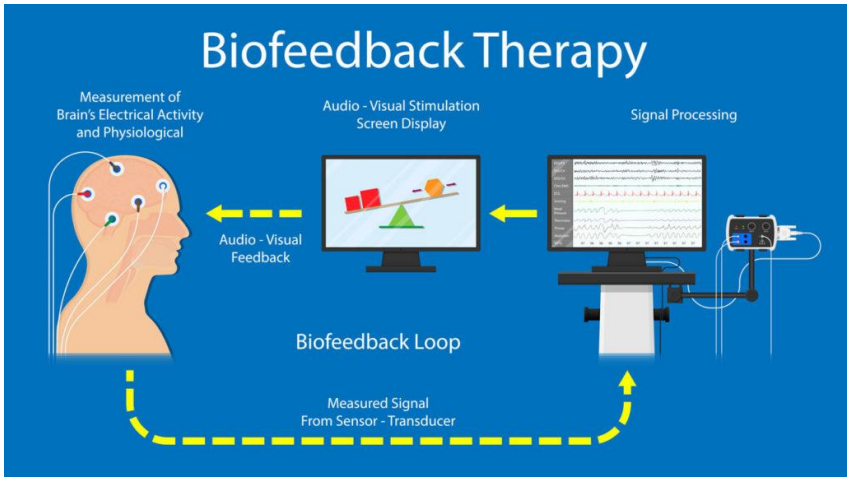

Figure 3: The Science of Neurofeedback Therapy in ADHD .

7. Nutraceutics

There has been growing interest in the roles of the n-3 polyunsaturated fatty acids (PUFAs) docosahexaenoic acid (DHA) and the precursor eicosapentaenoic acid (EPA) as potential treatments for ADHD symptoms. The longest-chain n-3 PUFA DHA is the most abundant PUFA in brain membrane phospholipids; it has an important role in membrane fluidity and associated metabolic and neural activities. DHA appears to be particularly concentrated at synapses, influencing dopaminergic, serotonergic, noradrenergic, and GABAergic neurotransmission [25]. Recent meta-analyses suggest that omega supplementation may improve ADHD symptoms to a modest degree, with an effect size of about a quarter as large as that seen for pharmacological treatment; whether sub-normal blood concentrations should be an indication for treatment is still not clearly established [26-28]. In summary, evidence from meta-analyses investigating RCTs of non-pharmacological interventions indicate that non-pharmacological treatments should not be recommended as the only interventions for core ADHD symptoms. The wider adoption of such approaches requires better evidence reported using blinded assessments [17]. This does not mean that pharmacological therapy necessarily represents the first choice for all subjects; in some children, psychosocial interventions alone are associated with recovery [29]. However, consistent evidence across studies confirms the utility of adding appropriate pharmacological therapy to existing psycho-social therapy, while only small benefits emerge from the addition of current psychosocial therapy to an ongoing drug treatment.

8. Pharmacological Treatments

Drug treatment for ADHD represents an intervention of specific value and relevance to patients within multimodal treatment. Methylphenidate (MPH), dexamphetamine, or amphetamine (AMP), derivatives, and 'noradrenergic' medications atomoxetine (ATX) and guanfacine are the most effective psychopharmacological treatments for ADHD. As a class the first three are usually referred to as stimulants.This is especially true in this case be-cause the objective of treatment in ADHD is almost the opposite of stimulation.

9. Drugs for ADHD:

AMP and MPH have been proved to be the most effective drugs for ADHD, their use is well established and consistently recommended in evidence-based clinical guidelines across the world (1-9), with a response rate of around 70%, rising to 95% when non-responders are treated with a second drug (30), It is a significant problem that amphetamine is a controlled substance as a result of the United Nations decree in 1971. In a number of countries, it is classed along with drugs like heroin, which has inevitably retarded its adoption for the treatment of children.

10. Molecular Mechanism of Action of Drugs for ADHD

AMP and MPH enhance the efflux and function of noradrenaline (NA) and dopamine (DA) in the CNS, with a rapid onset of action: they act by blocking (or even reversing) reuptake in their respective monoamine transporters [31]. AMP also increases catecholamine release from synaptic vesicles [32]. The therapeutic effects on be haviour and attention are presumed to be related to the enhanced neurotransmission of these catecholamine's, especially in the pre frontal cortex [33]. Racemic AMP (amethylphenetylamine) contains equal amounts of d-(dextroamphetamine) and

l-amphetamine isomers. In vitro, the affinity of AMP is higher for noradrenaline transporters (NETs) in the prefrontal cortex than for DA (in the striatum) [34]. MPH is significantly less potent than AMP at inhibiting vesicular accumulation of DA or NA, but a similarly potent inhibitor of synaptic reuptake of DA and a slightly less potent inhibitor of NA reuptake.

At therapeutic doses, DA and NA have a complementary effect on the firing rate of catecholamine neurons, which results in improved signalling, especially in the prefrontal cortex [35]. During cognitive tasks, MPH has been shown to increase cerebral blood flow in dorsolateral prefrontal and posterior parietal cortices in healthy controls and in the prefrontal cortex in adults with ADHD with a significant decrease in other regions. This suggests de-creased metabolic activation in task-irrelevant brain regions, with, in turn, more focused activation in task-relevant areas and improved performance [36-38]. More recently, drugs for ADHD have been shown to modulate functional connectivity; MPH normalizes activation and functional connectivity deficits in the brain networks supporting attention and motivation. This has been shown in medication-naïve children with ADHD during a rewarded continuous performance task, together with normalization of fronto-cingulate under-activation during error processing [39]. In adolescents with ADHD, the drugs demonstrated effects on the functional connectivity of fronto-parietal networks, with beneficial effects on working memory performance [40]. During inhibitory tasks, children with ADHD exhibit a raised motivational threshold at which task-relevant stimuli become sufficiently salient to deactivate the default mode network (DMN); treatment with MPH normalizes this threshold [41].

11. Pharmacokinetics

Absorption of AMP is rapid, with peak plasma levels about 3 hour after oral administration. AMP is metabolized through the liver be various P450 enzymes. Food does not affect total absorption but can delay it. Consistently with its pharmacokinetic profile, the onset of action release preparations, the duration of action is slightly longer than of AMP is rapid, within 1 hour after administration. For immediate-for MPH (around 405 hours), but still requiring at least twice daily administration to ensure adequate coverage, Mixtures of different d AMP and dl-AMP salt formulations (that is, Adderal) are available in the United States, but not in Europe. Lisdexamfetamine (LDX) is dextroamphetamine (DEX) covalent attached to the essential amino acid L-lysine, LDX itself is not thermodynamically active nor does it result in high DEX levels when injected or snorted, thus having a lower abuse potential Following oral administration, the amide linkage between the two molecules is enzymatically hydrolyzed, releasing active DEX. Most of this hydrolysis takes place within red blood cells. Pharmacokinetics of d-AMP after single-dose oral administration is linear, in adults, there is no accumulation of DEX at steady state nor accumulation of LDX after once-daily dosing for 7 consecutive days. The mean plasma half-life of d-AMP is about 11 hours. Oral MPH is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring about 1.5-3 hours after administration.

The elimination plasma steady half-life of d-three MPH is about 3-3.5 hours. Because of this short-half life, steady state for MPH is not achieved during regular treatment, although there is a theoretical possibility of steady state developing with high doses of extended-release preparations or in poor metabolizers. Classroom studies suggest a close relationship between the pharma-kinetic profile and pharmacodynamics properties [42]. Optimal clinical effect appears to be associated with rapidly increasing levels in the morning, followed by a steadily increasing plasma level across the rest of the day. Concerta XL, Matoride XL, Equasym XL, Medikinet Retard, and Ritalin LA' all provide a mixture of immediate and extended-release MPH, they differ in the mechanics of the delayed-release system and in the proportion of immediate-release to delayed-release MPH. Concerta XL' and Matoride XL effects last 10-12 hours, while Equasym XL, Ritalin LA', and Medikinet Retard can be considered mid-release formulations lasting between 6 and 8 hours. Transdermal patches (Daytrana) allow about 12 hours of effect if worn for 9 hours and are available in the United States. This for exhibits minimal first-pass metabolism, resulting in high bioavailability of MPH. Quillivant XR (5 mg/mL) is a recent long lasting liquid preparation of MPH. Peak plasma levels occur ap proximately 5 hours after dosing, with effects marketed to last for up to 12 hours. These differing delivery profiles provide the clinician with in-creased options when choosing which preparation to use. They allow a more flexible and sensitive individualized adjustment while retaining the benefits of an extended-release preparation Pharmacokinetic profiles may, however, show considerable inter Individual variation, and caution should be observed when generalizing from aggregated profiles to individual cases.

12. Interaction with Other Drugs

Drugs for ADHD show little interference with the metabolism and pharmacokinetics of other medications. There is, however, a potential to inhibit the metabolism of anticonvulsant drugs, such as phenobarbital, phenytoin, and primidone, and of tricyclic. Drug for ADHD may potentiate stimulating effects of other drugs on the Long cardiovascular or central nervous system and can increase pressor response to vasopressor agents. There are potentially dangerous interactions with substances of abuse like cocaine and other sympathomimetic agents, including ATX. For ADHD may potentiate stimulating effects of other drugs on the cardiovascular or central nervous system and can increase pressor response to vasopressor agents. There are potentially dangerous interactions with substances of abuse like cocaine and other sympathomimetic agents, including ATX.

13. Clinical Ffficacy

Strong evidence supports the efficacy of drugs for ADHD in reducing ADHD core symptoms over treatment periods of up to a year, and numerous placebo-controlled randomized trials confirm

their effectiveness in the short term, with effect sizes of between 0.8 and 1.1 on hyperactivity symptoms [2]. Drugs for ADHD reduce restlessness, inattentiveness, and impastivity, improving the quality of social interactions and decreasing aggression. Beneficial effects also extend to a broad range of associated functional impairments and comorbidities, including increased academic achievement, reduced risk of emergency admission to hospital for trauma, lower risk of depression and suicidal events, and decreased rates of substance abuse and criminality, Knowledge about the effectiveness of medication in ADHD children and adolescents has also been expanded in specific populations, Within the Preschoolers with ADHD Treatment Study (PATS trial, 160 children younger than 6 years were randomized to placebo or immediate-release MPH. The magnitude of MPH effect (dos range 2.5-7.5 mg) was lower than typically observed in school-age children, with an increased frequency and severity of adverse event (that is, greater mood liability or reduced growth rate and treatment discontinuation in about 11% of cases) [43-49]. Positive results, but with more frequent and severe adverse effect have also been observed in ADHD children with comorbid autism spectrum disorder (ASD). A meta-analysis showed MPH to be effective (effect size 0.67) for treating ADHD symptoms in children with pervasive developmental disorders, but its relatively lower to tolerability must be taken into account [50]. Although early studies suggested that children with comorbid anxiety or internalizing symptoms displayed lower response rat on ADHD symptoms, more recent studies, including the MT study, do not support this. Drugs for ADHD at a group level show beneficial effect on anxiety, and several recent studies show that they are quite effective in controlling ADHD in the context Tourette's disorder. A recent meta-analysis also shows that MPH is clearly an potential therapeutic option for comorbid disruptive behavioral problems and aggression in patients with ADHD and comorbid disorder. Studies of MPH efficacy on aggression in conduct disorder without ADHD are still lacking [51,52]. LDX has been shown to be more effective than placebo on AD symptoms (effect size 1.8). LDX was also effective in treating problems associated with ADHD, significantly improve quality of life [53]. The randomized withdrawal of treatment 24 weeks of open-label treatment indicated the continued bene LDX treatment, with treatment-emerging adverse events general consistent with those associated with the MPH preparation, use the active comparator [54].

14. Long-Term Efficacy of Drugs for ADHD

Although the short-term benefit of drugs for ADHD has been repeatedly confirmed within several studies, its long-term effects have been less well investigated. The MTA study still represents the most valid source of information on the long-term effects of MPH Within this large-scale, random-allocation, non-blind trial, a comparison was made between careful medication management, intensive behaviorally oriented psychosocial therapy, a combination of the two, and a simple referral back to community (usually medication) [10]. The main conclusions after 14 months were that careful medication was more effective than Behavioural treatment. The combination of Behavioural therapy and medication have some benefits: better control of aggressive behaviour at home, improved overall sense of satisfaction of parents, and possibly reduced medication dosage. The follow-up at 36 months, by which time parents and children were free to choose the actual treatment, showed that all four original groups had a similar outcome; similar results were observed at up to 16 years' follow-up [55]. Various explanations are possible-the effects of more intensive therapy disappear when intensive treatment is stopped; self-selection of patients to treatments at the end of the randomization phase may lead to similar outcome (many children assigned to Behavioural intervention started medication, and a significant percentage of those on intensive medication management actually withdrew medication). The most favourable overall development was found in children initially randomized to the MTA medication regime, whether or not they were taking medication at 36 months, thus suggesting some lasting benefit for some children with ADHD.

15. Non-Dopaminergic Medications

Currently, two classes of non-dopaminergic agents are approved for ADHD treatment: the selective NA reuptake inhibitor ATX and the 2 agonists guanfacine and clonidine. The main clinical differences between these agents and dopaminergic drugs are their more favourable legal status, their potential for a long (up to 24 hours) duration of clinical efficacy, and a generally slower onset of action (at least several weeks).

16. Mechanism of Action and Pharmacokinetics

ATX is a selective inhibitor of NA synaptic reuptake. In vitro, it shows high affinity with NETs, and in vivo, it induces an increase in NA extracellular concentrations in the prefrontal cortex. In this region, despite its low affinity for its transporters, it also results in a strong increase in the extra neuronal concentration of DA, which remains stable in the nucleus accumbency and striatum making abuse or triggering of tics by ATX unlikely. ATX is metabolized mainly through the hepatic cytochrome P450 2D6 enzymatic system (CYP2D6), resulting in metabolites with clinically significant activity. Once-daily ATX is associated with a decrease in 3,4-dihydroxyphenylethylene glycol (DHPG), which is the main brain metabolite of NA and a biomarker of central NET inhibition, persisting for at least 24 hours. Interestingly, there also appears to be a dissociation between the pharmacokinetic and pharmacodynamics profiles for ATX, with evidence that, despite the relatively short half-life, even once-daily dosing can result in clinical effects lasting throughout the day [56].

Guanfacine is a selective 42 noradrenergic agonist, with 15-20 times higher affinity for a2A adrenergic receptors than for a28 or a2C receptors. Extended release guanfacine (matrix-s tablets, GXR) is well absorbed, after oral administration, the time to peak plasma concentration is approximately 5 hours. GXR half-life is 16-17 hours. Allowing once daily administration. The pharmacokinetic profile of guanfacine is linear (first-order) and dose-proportional. The profile of GXR differs from that of

immediate-release (IR) guanfacine, with GXR resulting in 60% lower C, and up to 43% lower area under the curve (AUC), compared to IR tablets Clonidine is an a2 receptor agonist, which modulates adrenergic transmission. Reducing sympathetic activity can give rise to hypo-tension, sedation, and irritability. Clonidine appears to be less efficacious than conventional drugs in the treatment of ADHD. The effectiveness in reducing tics in children with ADHD is comparable to dopaminergic drugs. In addition to the effects of sedation and symptomatic hypotension, clonidine can cause bradycardia and dry mouth [57].

17. Clinical Efficacy of Non-Dopaminergic Medications

The clinical efficacy of ATX has been well documented in short- and long-term studies, with an effect size of approximately 0.7 across studies [58, 59]. The onset of clinical effectiveness of ATX is slower than that of dopaminergic drugs, varying between 2 and 4 weeks. Full therapeutic effect can take up to 6-8 (or even 12) weeks, but responders typically show some degree of improvement by 4 weeks [60]. Some patients may continue to improve for 36 weeks [61]. Guanfacine showed significant improvement of clinician and teacher-rated symptoms, functional impairment, and positive continuous performance outcome measures in a series of controlled trials [62]. A recent randomized withdrawal trial showed long-term maintenance of efficacy [63]. In adults, guanfacine modulates the influence of emotion control on cortical activation for cognitive control [64].

18. Other Drugs

Bupropion acts as a weak inhibitor of presynaptic reuptake of NA, DA, and 5-HT; it has been licensed for depression and smoking cessation. It showed better efficacy than placebo in reducing ADHD symptoms in children, although lower than dopaminergic drugs. Bupropion can cause nausea, insomnia, and palpitations; it can also trigger tics and cause dermatological reactions, at times severe enough to lead to discontinuation of the drug. Three head-to-head trials found bupropion had efficacy comparable to that of MPH, al-though a large double-blind, placebo-controlled multicentre study found smaller effect sizes for bupropion, compared to MPH. In terms of tolerability, a head-to-head trial found that headache was more frequent in the MPH group than in the bupropion-treated group, with no difference in other adverse events [65]. Tricyclic antidepressants: the mechanism of action of tricyclic involve inhibition of presynpatic NA reuptake, with poor selectivity. None of them is approved by the FDA or European Medicines Agency (EMA) for the treatment of ADHD; they were prescribed off-label for children with ADHD, but after the introduction of ATX, they are rarely used because of concerns about their potential cardiovascular toxicity. Modafinil is a 'wakefulness-promoting agent' marketed for the treatment of narcolepsy; it has been occasionally used for the management of inattention in Adults. Its mechanism is poorly de-fined as a non-dopaminergic activating action on the frontal cortex. A recent meta-analysis on five RCTs showed an effect size of 0.7 on ADHD symptoms and a significantly higher incidence of decreased appetite and insomnia, but non-significant cardiovascular adverse events, compared to placebo [66].

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect[a]	Duration of Effect	Comments	References
Norepinephrine transporter reuptake inhibitor								
Long 	Atomoxetine	Strattera	Children ≥6, adults	1-2	3-4 wk	NA[b]	Dosed by body weight	34, 35
$Alpha_2$-adrenergic receptor agonist								
Long 	Clonidine HCL	Kapvay	Children ≥6	2	2 wk	NA	An antihypertensive agent May be prescribed in addition to a stimulant Discontinuation must be gradual	36, 37
$Alpha_{2A}$-adrenergic receptor agonist								
Long 	Guanfacine	Intuniv	Children ≥6	1	3 wk	Up to 24 h per dose	An antihypertensive agent Dosed by body weight May be prescribed in addition to a stimulant	38, 39

Figure 4: FDA-Approved Nonstimulant Medications for ADHD

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Amphetamine								
Short	Amphetamine mixed salts	Adderall	Children ≥3	1–3	1.5 h	4-6 h	Elimination half-life 9.77-11 h for the D-isomer and 11.5-13.8 h for the L-isomer	13–15
Intermediate	Racemic amphetamine sulfate	Evekeo	Children ≥3 (tablet) Children 6-17 (ODT)	1–2	45 min	9.25 h	Elimination half-life 10.0-11.7 h	16–18
Long	Amphetamine mixed salts	Adderall XR	Children ≥6, adults	1	1.5 h	10.5–12 h	May be sprinkled on applesauce	19, 20
Long	Amphetamine	Adzenys ER	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Do not add to food or other liquids	21
Long	Amphetamine	Adzenys XR-ODT	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Allow tablet to disintegrate in saliva before swallowing	22
Long	Amphetamine	Dyanavel XR	Children ≥6	1	1 h	12 h		23
Long	Amphetamine mixed salts	Mydayis	Children ≥13, adults	1	2 h	14 h	May be sprinkled in applesauce	24, 25
Long, prodrug	Lisdexamfetamine dimesylate	Vyvanse	Children ≥6, adults	1	1.5-2 h	12–14 h	Capsule: may be sprinkled in water, orange juice, or yogurt Chewable tablet: chew thoroughly before swallowing	26, 27
Dextroamphetamine								
Short	Dextroamphetamine sulfate	Dexedrine	Children 3-16	1–2	NA	4–6 h		14, 28
Short	Dextroamphetamine sulfate	Zenzedi	Children 3-16	1–3	NA	4–6 h		29
Short	Dextroamphetamine sulfate	ProCentra	Children 3-16	1–3	NA	4–6 h		30
Intermediate	Dextroamphetamine sulfate	Dexedrine Spansule	Children 6-16	1–2	NA	6–10 h	Plasma half-life of approximately 12 h	14, 28
Methamphetamine								
Short	Methamphetamine HCL	Desoxyn	Children ≥6	1–2	NA	NA	Not readily available	31

Figure 5: FDA-Approved Amphetamine Formulations for ADHD.

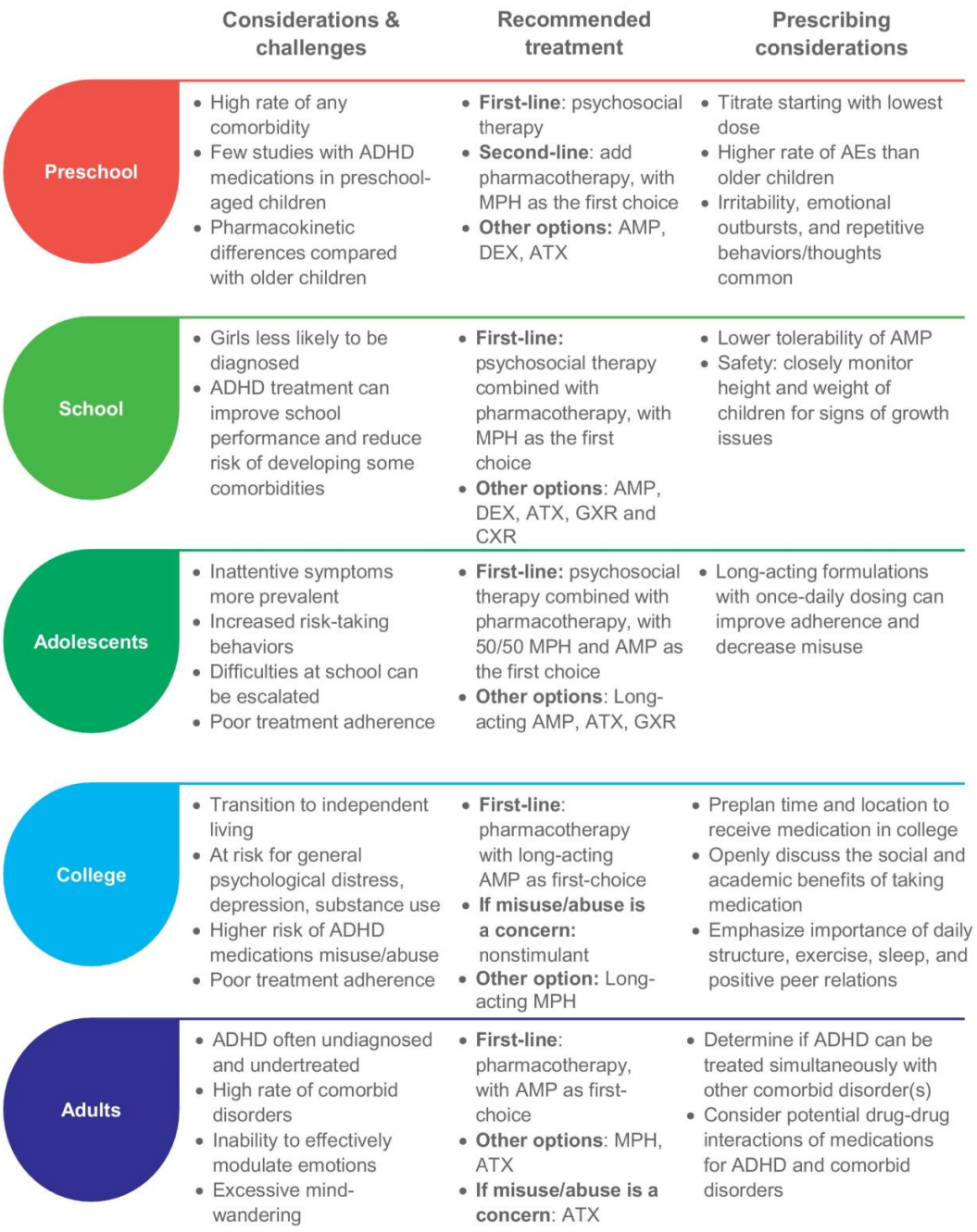

Figure 6: ADHD Treatment Guide by Age Group.

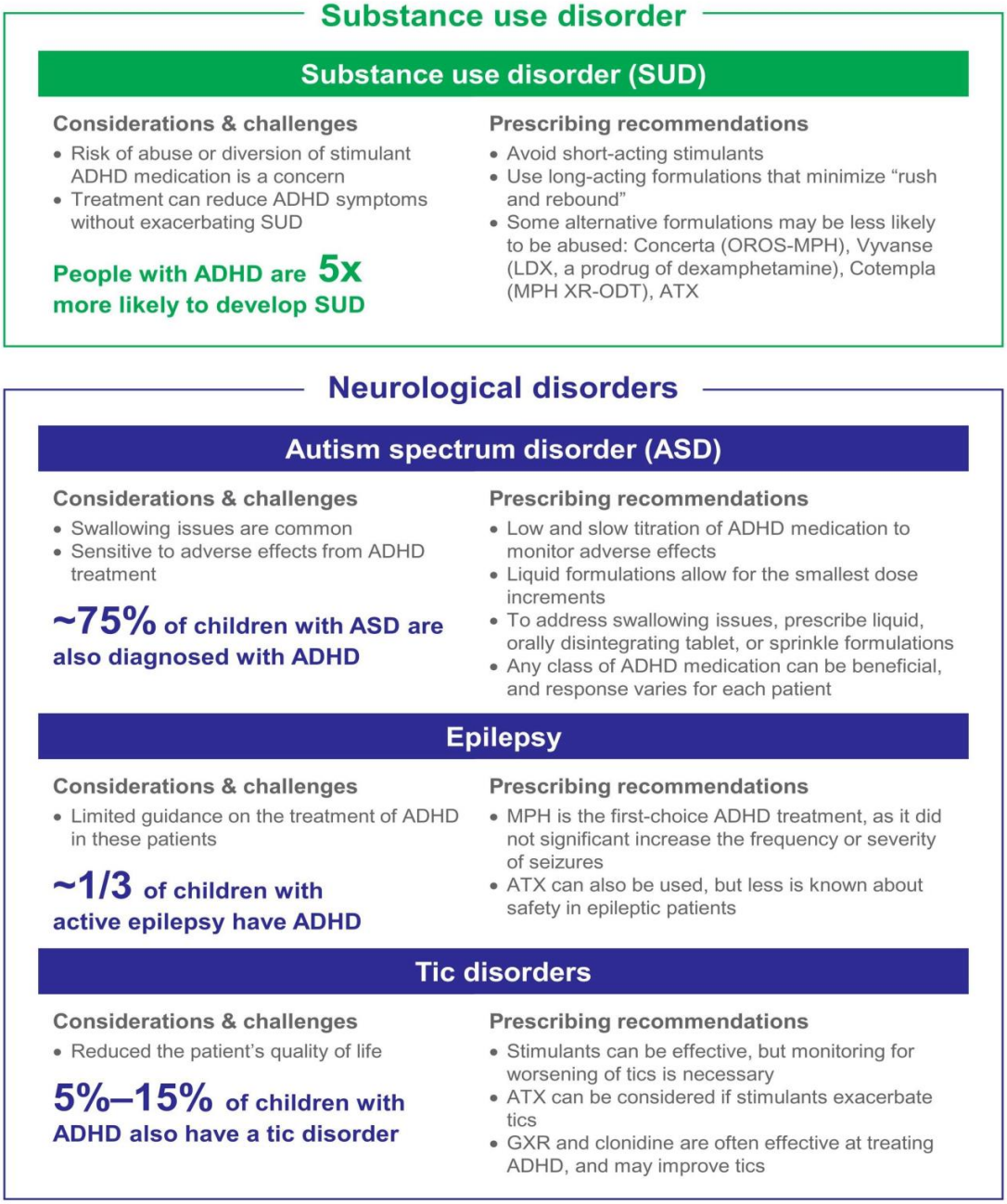

Figure 7: ADHD Treatment Guide by Comorbid Condition.

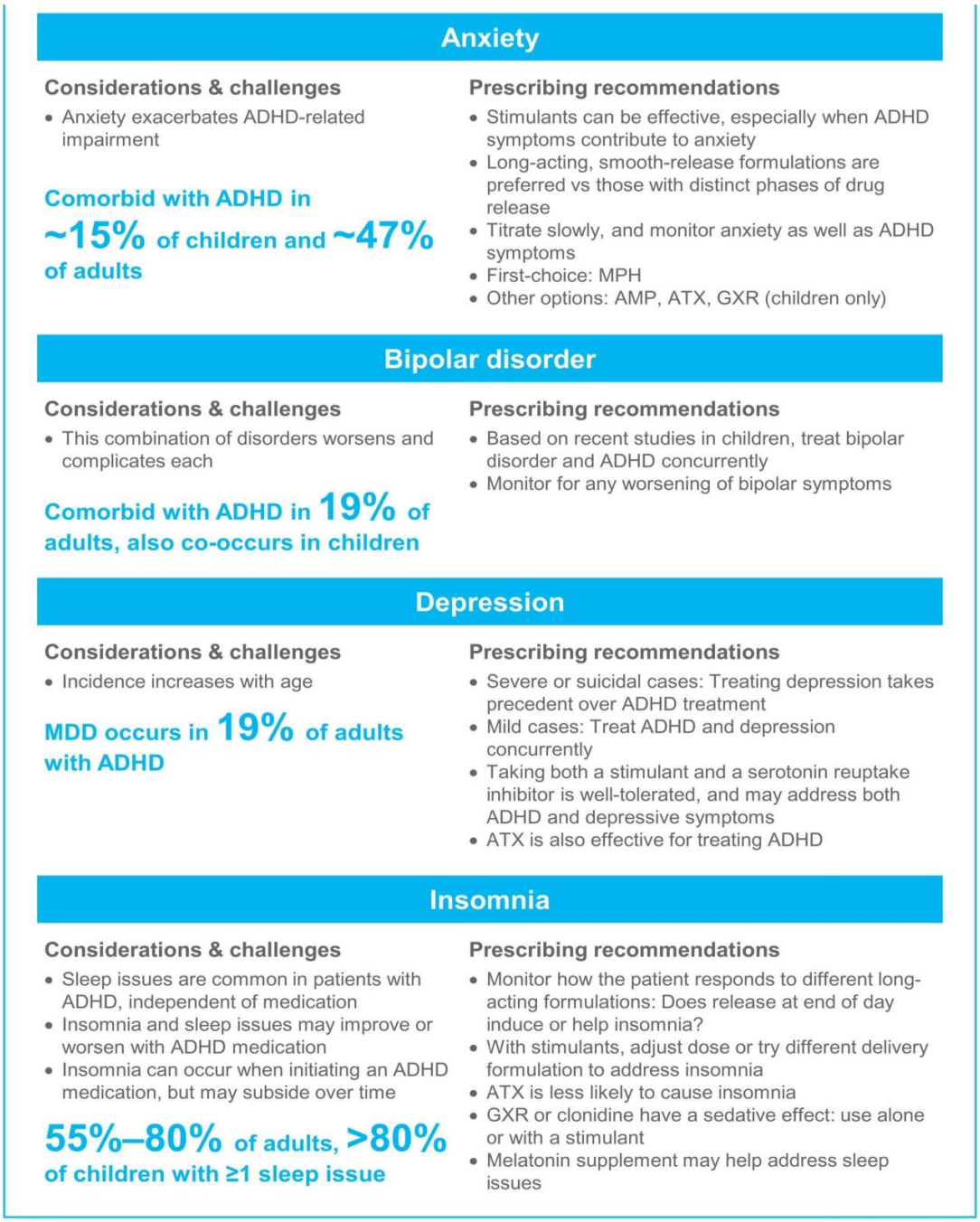

Figure 8: ADHD Treatment Guide by Comorbid Psychiatric Condition.

19. Medication Safety and Management of Adverse Effects

Medications for ADHD are generally safe and well tolerated; adverse effects are mild, transitory, reversible, and easily manageable by the ADHD specialist [3,41]. The most common side effects of dopaminergic agents include sleep difficulties, irritability, appetite and weight loss, headache, tachycardia, and increased blood pressure (BP) and heart frequency. Side effects of non-dopaminergic drugs mainly include nausea, sedation, and appetite loss, dry mouth, insomnia, constipation, and mood swings. Additionally, urinary retention and sexual dysfunction have been observed in adult patients. Most of these adverse effects diminish over the first months of treatment, with no significant differences between normal and poor metabolizers [2]. More severe adverse reactions, like psychotic symptoms or allergic reactions, have rarely been observed in association with dopaminergic or non-dopaminergic medications [3,4]. Despite this, the tolerability and

safety of medications used to treat ADHD have recently been raised as a concern to some regulatory authorities. In January 2009, the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) concluded that the – benefit of MPH outweighs the risk when prescribed to ADHD children over 6 years and recommended to standardize prescribing and to provide safety information across all EU members. They further concluded that research was needed on the long-term effects of MPH [67]. As a result of these recommendations, the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) consortium was established to confirm MPH safety; it included experts in the fields of ADHD, drug safety, neuropsychopharmacology, and cardiovascular research (http://www.adhd-adduce.org).

20. Cardiovascular Effects

MPH, AMP, and ATX are sympathomimetic agents that increase noradrenergic and dopaminergic transmission; an effect on heart activity [68, 69]. MPH and ATX may be associated with rate (HR) and BP is therefore an intrinsic feature of their pharma-generally small elevations of BP (≤5 mmHg) and HR [≤10 beats/minute (bpm) at a group level: a subset of children and adolescents (around 5-15%) may experience greater treatment-related increases in HR or BP, over the 95th centile, or may report a cardiovascular type complaint during drug treatment [69]. The 10-year follow-up of the MTA study found no effect of treatment on either systolic or diastolic BP; however, use of dopaminergic drugs was associated with a higher HR at years 3 and 8. A recent meta-analysis conducted in ADHD children and adolescent treated with MPH, AMP, or ATX, including 18 trials with data from 5837 participants (80.7% boys) and an average treatment duration of 28.7 weeks, revealed that all three medications were associated with a small, but statistically significant, pre-post-increase of systolic BP (SBP). Compared to AMP and ATX, MPH did not show a pre-post-effect on diastolic BP (DBP) and HR. Only 2% of patients discontinued their medication due to any cardiovascular effect. In majority or with medication dose changes [70,71].

A meta-analysis in adult patients with ADHD reported that treatment is associated with the majority of patients, the cardiovascular effects resolved, but significant, increases in SBP (+2.0mmHg) and HR (+5.7 including PR, ORS, and QT intervals, have been associated with the bpm), but no effect on DBP [72]. No changes in ECG parameters, but persistent, BP and/or HR increases may increase the risk for ser-use of MPH and ATX 69. However, it is a concern that even small, cardiovascular events, including sudden cardiac death, acute myocardial infarction, and stroke, in the long term. The magnitude of this risk remains to be established. The available epidemiological studies, summarized by Hammerness et al., do not show a significant association between ADHD drugs and serious cardiovascular events. A recent large study of 1.200.438 children and young adults between 2 and 24 years found no evidence that ADHD drugs increased the risk of serious cardiovascular events 73 [65].

Similarly, several large registry guides of adults and children (3-17 years) suggest that ADHD medication, when medically supervised, was not associated with an increased risk of severe cardiovascular events. Current guidelines [3] recommend that patients being considered for ADHD medication should have a clinical assessment, including identification of any known heart disease, any history of syncope with exercise, and any family history of sudden unexpected deaths under the age of 40 years. HR and BP should be taken at baseline and repeated every 3-6 months. It is important to make a referral for fur ther assessment when indicated, and for patients with pre-existing cardiac conditions, dopamine or NA-releasing drugs should be use cautiously and only after consultation with a cardiologist [74,75].

21. Growth and Developmental Effects

One of the most common side effects of drugs for ADHD is appetite with prolonged use. The mechanism by which growth is loss, with consequent reduced weight gain and possible growth affected has not yet been fully clarified. The decrease in appetite and the consequent reduction in caloric intake represent the obvious include medication effects on hepatic and/or CNS growth probable cause of the growth slowdown [76]. Other possible factors and direct effects on cartilage. Studies providing longitudinal data suggest the height deficit is approximately 1 cm/year during the first 3 years of treatment, while some other data suggest that these effects tend to attenuate over time and ultimate adult growth parameters are [72,77]. generally not affected In the recently published MTA follow-up into adulthood, prolonged use of MPH in the ADHD group resulted in an average height of 1.29 ± 0.55 cm shorter than the control group ($p < 0.01$, $d=0.21$). Within the treated sample, adherence to drug treatment was classed as consistent, inconsistent, or negligible: participants with the consistent or inconsistent pattern were 2.55 ± 0.73 cm shorter than the subgroup with the negligible pattern ($p < 0.0005$, $d=0.42$) [55].

Preliminary analysis of the large 2-year naturalistic pharmacovigilance ADDUCE study shows a lower height velocity standard deviation score (SDS) in medicated ADHD subjects than in undedicated ones, roughly equivalent to a reduction in height velocity of about 0.35 cm/year for a 9.6-year-old boy (mean age of subjects in the study) [67]. In post analyses, the impact on a child's height velocity SDS was apparently associated with the severity of illness, suggesting a possible dose-dependent effect of MPH. With regard to ATX, a meta-analysis of seven double-blind/placebo-controlled and six open-label studies found that the mean actual weight and height at 24 months were, respectively, 2.5 kg and 2.7 cm lower than the expected values [78]. The difference occurred mostly during the first 18 months of treatment. In order to prevent growth suppression and ensure an adequate growth pattern to subjects in the age of development, current guide-lines recommend:

• Monitoring appetite, weight, height, and BMI every 6 months [3].
• Differentiating between pretreatment eating problems and medication-induced eating problems.
• Giving medication after meals, rather than before.
•Encouraging the use of high-calorific snacks and late evening meals.
• Reducing the dose or switching to an alternative class or formulation.
• Discontinuing medication on weekends to prevent weight loss or longer drug holidays to allow for catch-up growth.
• Referring to a paediatric endocrinologist/growth specialist if height and weight values are below critical thresholds.

22. Neurological Effects

Drugs for ADHD might, from a theoretical point of view, exacerbate tic severity as they can increase DA activity in the basal ganglia [79] A meta-analysis, including nine DBRPC trials, examining the efficacy of medications for ADHD in children with comorbid tic (a total of 477 subjects) concluded that MPH does not worsen tic severity the short term, although it is possible that MPH may worsen tics individual cases and that ATX can, on the other hand, significant improve comorbid tics [80]. The recent Cochrane group systematic review [81] concluded the same. With regard to ATX, although can have a positive effect on tic frequency, some case reports ha described exacerbation of tics during ATX treatment [4]. Thus, t are no longer a contraindication for the use of ADHD drugs in EU, but caution is still recommended [82] (EMA, 2010). The management of tics should include: (1) observation of the density of tics over a 3-month period before any decision regard ADHD treatment; (2) dose reduction; (3) substitution; and (4) if previous measures are not effective, an antipsychotic can be ad to control tics.

23. Sleep Problems

Sleep problems are common in individuals with ADHD, and also important to rule out primary sleep disorders that may m or exacerbate ADHD. Both AMP and MPH may increase the la to sleep onset, shorten sleep duration, and decrease sleep [83]. It is necessary to assess sleep at baseline and to monitor throughout treatment, as all ADHD medications sleep. Dose timing adjustments, switching drug formula or adding an evening dose of melatonin are often helpful str for drug-exacerbated insomnia in children displaying a good cation response [84]. Seizures and epilepsy Although longer-term effects of MPH and its effects in children with frequent seizures need further study, current evidence supports the use of MPH for the treatment of ADHD in patients with well-controlled epilepsy and even in those with infrequent seizures [85]. When epilepsy is poorly controlled, the frequency of seizures should be carefully monitored; if their frequency increases, or seizures develop, then ADHD medication should be stopped.

24. Psychiatric Effects

Psychotic, mood, and other psychiatric symptoms Drugs for ADHD have been associated rarely with possible severe psychiatric effects, including psychotic symptoms (hallucinations). A review of the literature does not strongly indicate an association between MPH treatment for ADHD and psychosis. However, some open-label trial extension studies reported discontinuations due to psychotic symptoms. In contrast, some positive clinical experience (drugs for ADHD being helpful) have been reported for managing ADHD symptoms in the context of a psychotic disorder. A single study also found that medication with MPH in childhood could show a protective effect by reducing schizotypic features in adults. Suicide-related events have also been investigated during treatment with drugs for ADHD, with symptoms sometimes anecdotally improving following discontinuation of medication. A recent population-based electronic medical records study showed that, in fact, the incidence of suicide attempts was higher in the period immediately before the start of MPH treatment.

The risk remained elevated immediately after the start of MPH treatment but returned to baseline levels during continuation of the treatment. The observed higher risk of suicide attempts before treatment may reflect emerging psychiatric symptoms that trigger medical consultations, resulting in MPH treatment [86]. Population-based studies indicate that medication for ADHD is associated with a reduced long-term risk (that is, 3 years later) for depression [45] and a potential protective effect on suicidal behaviour [87]. However, individual patients being treated with medications for ADHD should be observed for the emergence of psychotic symptoms, depression, irritability, and suicidal ideation, as part of routine monitoring. Mood liability, dysphoria, anxiety, hostility, and explosive out-bursts may be observed in 5-10% of children taking drugs for ADHD. Among children whose aggressive behaviour develops in the context of ADHD and oppositional defiant disorder or conduct disorder, systematic, well-monitored titration of monotherapy often reduces aggression considerably, thus averting the need for additional medications [88].

25. Substance Misuse

DA-releasing drugs have the potential for misuse and can be diverted by patients or families to this end [89]. The extended-release formulations of drugs for ADHD are less prone to diversion, because they do rapidly increase blood drug levels and are also less easily crushed into powder for injection or snorting. Once-a-day administration also makes parental supervision easier to enforce. Non-dopaminergic medications (that is, ATX) are another option with low abuse potential. Concern has been raised that therapeutic use of drugs for ADHD may result in ‘sensitization’ and possibly increase the risk for sub-stance use disorder (SUD) later in life. However, ADHD is associated with impulsivity and conduct disturbances, and represents itself a risk factor for SUD. Naturalistic follow-up studies do not support the contention that drugs for ADHD increase the risk for SUD (for example, Swedish registry studies found drug treatment associated with decreased rates in patients with ADHD) [48].

26. Management and Treatment of ADHD in Adulthood

ADHD is a chronic condition with symptoms frequently persisting into adulthood. About 60% of affected children have, as adults, significant ADHD-related impairments, including social dysfunction, educational and occupational underachievement, substance abuse, increased risk for accidents, and legal difficulties [90]. Although awareness, recognition, and diagnostic criteria of ADHD in adults have improved in recent years, there is still the need to increase physician support and specialized services for the clinical management of this disorder, as patients make the transition to the adult health care system [91, 92]. The NICE guidelines in the UK provide strong support for the provision of adult ADHD services, recommending that young people with ADHD and receiving treatment from child and adolescent mental health services (CAMHS) or paediatric services should be reassessed at school leaving age to establish whether treatment should continue into adulthood. Adult ADHD symptomatology differs from the typical childhood presentations, hyperactivity/impulsivity may diminish over time. While inattention tends more often to persist, with a greater impact in adults.

Optimal strategies for ADHD in adulthood are, as in child. Hood, multimodal, with the main goals of improving symptoms and optimizing functional performance [93]. Adults respond well to the same classes of medication used in children, and MPH and AMP are confirmed as first-line pharmacologic interventions [94]. Adults with = ADHD have, in fact, reported improved social relationships, aca demic/work functionality, and driving, together with reduced criminal behaviour, as a consequence of ADHD medications [95]. Additionally, adults with ADHD treated with drugs prior to 18 years have been shown to have better outcomes across broad quality of life measure-ments, as compared with subjects not previously so treated [96]. Just as for children and adolescents, drug treatment of adult ADHD consistently yields positive short-term effects, but few trials have evaluated their long-term efficacy and safety. Poor compliance and comorbid psychiatric disorders may further complicate the de-termination of treatment benefits in adults with ADHD [97]. ADHD medications can cause side effects also during adulthood.

The most worrying include increases in both BP and HR. However, as con-firmed by a recent large population cohort study [70], there is no increased risk for acute myocardial infarction, sudden cardiac death. Or stroke for current ADHD medication users, compared to non-users. While the risks of serious side effects are thought to be low for healthy adults, physicians should, however, be cautious when pre-scribing for patients with cardiovascular disease, seizure disorders, and psychosis [98]. Even though pharmacologic interventions are considered first-line treatments for ADHD, some adults with ADHD continue to experience significant residual and impairing symptoms. CBT has been shown helpful in the treatment of adult ADHD. Alone and in combination with psychopharmacology [99]. Another psychoeducational approach that has gained increasing popularity in the last year is coaching. It is a highly individualized intervention, in which a personally assigned coach guides the patient in accomplishing tasks and goals. Coaching differs from traditional CBT, because it is more focused on solving specific problems of reaching specific goals and is more accessible to the patient on an as-needed basis [100].

27. Conclusions

ADHD is a chronic, heterogeneous condition, with a high prevalence impairment extending beyond the affected individual. Established efficient assessment methods and good treatment evidence help clinicians in monitoring and managing this disorder in childhood and adulthood. ADHD drugs, available in different formulation, are, especially in the short term, currently among the more effective drugs in psychiatry and perhaps in general medicine a good safety profile. Long-term treatment efficacy and, with a tolerability and safety data are still insufficient and need more re-search. On the basis of the current evidence, however, there does not seem to be any necessity to change current clinical guidelines for the monitoring of the main possible adverse events [101].

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