Review

Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders

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Abstract

Objectives: To date, there is no single medication prescribed to alleviate all the core symptoms of Autism Spectrum Disorder (ASD; National Institute of Health and Care Excellence, 2016). Both serotonin reuptake inhibitors and drugs for psychosis possess therapeutic drawbacks when managing anxiety and aggression in ASD. This review sought to appraise the use of propranolol as a pharmacological alternative when managing emotional, behavioural and autonomic dysregulation (EBAD) and other symptoms.

Materials and methods: Sixteen reports examined the administration of propranolol in the context of ASD.

Results: Sixteen reports broadly covered cognitive domains, neural correlates, and behavioural domains. From the eight single-dose clinical trials, propranolol led to significant improvements in *cognitive performance* – verbal problem solving, social skills, mouth fixation, and conversation reciprocity; and changes in *neural correlates* – improvement in semantic networks and functional connectivity. The remaining eight case series and single case reports showed improvements in EBAD, anxiety, aggressive, self-injurious and hypersexual behaviours. Additionally, propranolol significantly improved similar behavioural domains (aggression and self-injury) for those with acquired brain injury.

Conclusion: This review indicates that propranolol holds promise for EBAD and cognitive performance in ASD. Given the lack of good quality clinical trials, randomised controlled trials are warranted to explore the efficacy of propranolol in managing EBAD in ASD.

Keywords

Autism Spectrum Disorder, ASD, propranolol, beta-blockers, anxiety, aggression, EBAD

Introduction

Autism Spectrum Disorder (ASD) has an estimated prevalence of 1–2.4% (Baron-Cohen et al., 2009; Zablotsky et al., 2015a), with approximately 1 diagnosis per 68 children (Wingate et al., 2014). Core features of ASD are characterised as impairments in social interaction, verbal and non-verbal communication and restricted and repetitive patterns of behaviour (American Psychiatric Association, 2013; Kendall et al., 2013; Ospina et al., 2008; Tsai, 1999). ASD is associated with long-term psychosocial impairment (Billstedt et al., 2005) and substantial burden on the individual, their family and caregivers, in addition to social and economic burden (Knapp et al., 2009; Lecavalier et al., 2006). Among others, concerning behaviours that commonly occur in ASD include aggression, anxiety, phobias, hyperactivity, compulsive behaviour, depression, suicidal ideation or attempted suicide and sleep disorders (Brereton et al., 2006; Cassidy et al., 2014; Simonoff et al., 2008; Stewart et al., 2006). Anxiety disorders frequently present in children and adolescents with ASD, with comorbidity ranges of 40–84% for any anxiety disorder, 8–63% for specific phobias, 5–23% for generalised anxiety, 13–29% for social anxiety and 8–27% for separation anxiety (White et al, 2009; Sukhodolsky, 2013). Other studies suggest that anxiety disorders and/or heightened aggression occur in 40% and 56% of children and adolescents with ASD, respectively (Kanne and Mazurek, 2011; van Steensel et al., 2011). Moreover, anxiety in children and adolescents may also contribute to other mood disorders, particularly for depression and bipolar disorders (Cummings and Fristad, 2012).

The National Institute of Health and Care Excellence (NICE, 2016) guidelines highlight that we do not currently have medication that can be prescribed to address the core features of ASD. Clinically, the established practice is to target the symptoms of the comorbid conditions associated with ASD, such as hyperactivity, irritability, psychosis, depression, aggression and repetitive behaviours (Nevels et al., 2010; Robb, 2010; Santosh and Singh, 2016), as well as co-occurring psychiatric diagnoses (Zablotsky et al., 2015b). Although there are varying amounts of

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empirical evidence for targeted pharmacological interventions, drugs for depression/psychosis, anticonvulsants and stimulants are routinely used to treat comorbidities associated with ASD in children and adolescents (Bauman, 2010; Canitano and Scandurra, 2011; Kumar et al., 2012; Santosh and Singh, 2016; Williams et al., 2013). Despite the extremely common use of these medications, there is a dearth of evaluable information to address their efficacy in treating the core symptoms of ASD. Holistic multimodal treatments are essential for the management of ASD. Treatment programmes such as psychosocial, language and behavioural therapies are not covered in this review, but it would be necessary to use them in conjunction with medication (Santosh and Singh, 2016).

Perhaps the most frequent and detrimental comorbidity associated with ASD is aggression. Drugs for psychosis have been used to treat it and most studies report side effects that are problematic in the long term. Similarly, drugs for psychosis result in either motor or metabolic side effects including excessive sedation, tardive dyskinesia (TD) (McDougle et al., 2003), and increased appetite and/or weight gain (Francis, 2005). These are significant side effects in children and adolescents with anxiety and ASD (Aman, 2004; Leskovec et al., 2008).

Despite a lack of clear evidence, currently, anxiety in ASD involves a cautious trial of serotonin reuptake inhibitors (SERTs), including sertraline, fluoxetine, fluvoxamine and citalopram; or risperidone if there was poor response. Treatment with SERTs are often associated with increased irritability, insomnia, nausea and/or weight gain (Francis, 2005; Leskovec et al., 2008). One would need to monitor for worsening of anxiety in some children. Obviously, the decision on treatment needs to be made on a case-by-case basis (Santosh and Singh, 2016). It is therefore essential that other pharmacological agents are investigated (Reinblatt and Riddle, 2007).

Alongside ASD, organic neuro-behavioural disorders, such as acquired/traumatic brain injuries (ABIs), organic brain diseases, intellectual disability, personality disorders, forms of psychosis, attention-deficit hyperactivity disorder and post-traumatic stress disorder, can also present with poor social skills, high anxiety, irritability and aggression. There is extensive literature in this group of subjects, and β-blockers, particularly propranolol, are now considered a recommended treatment in this group (Chew and Zafonte, 2009; Fleminger et al., 2006; Greendyke et al., 1986; Haspel, 1995; Newman and McDermott, 2011; Thibaut and Colonna, 1993). These difficulties may mirror symptoms in ASD, as emotional and behavioural difficulties are customary in ASD (Berkovits et al., 2017; Samson et al., 2014). Similarly, autonomic dysregulation occurs within the context of ASD, whereby symptoms of hyperarousal leading to explosive rage, elevated heart rate, rapid breathing, and other atypical physiological responses are observed (Ming et al., 2016). Psychiatrists are good at focusing on emotional and behavioural dysregulation, but rarely assess or manage associated autonomic dysregulation. Autonomic dysregulation is often seen in organic brain disorders (Kanjwal et al., 2010; Zamzow et al., 2016), ASD, and treatment-resistant patients. Often, treating the autonomic dysregulation assists in converting the patient into a treatment responder (Santosh et al., 2017). Considering this, emotional, behavioural and autonomic dysregulation (EBAD) is a target area for pharmacological interventions, and has been demonstrated to be a viable treatment strategy in the management of rare diseases (Singh and Santosh, 2017).

Propranolol is a non-selective β-blocker competing for beta-adrenergic receptors inhibiting the action of noradrenaline and adrenaline (Agrawal, 2014). Typically, propranolol is absorbed completely after oral administration, with around 90% being eliminated via the liver. Subsequently, propranolol has a low yet varied bioavailability due to variation in the user's plasma levels and liver function (Johnsson and Regårdh, 1976; Shand, 1976). Propranolol has a half-life of around 2–4 hours (Johnsson and Regårdh, 1976), yet varies considerably depending on age, sex, and blood plasma levels (Gilmore et al., 1992). Traditionally, propranolol is used to treat hypertension and angina with reduced risk of coronary heart disease and tachyarrhythmia (Kiriyama et al., 2016) and is commonly used to treat migraine (Ahmed et al., 2016). Propranolol is contraindicated in those with bronchial asthma or those prone to bronchospasm, as it would increase bronchospasm. Considering propranolol is non-selective, these effects carry over to the β-cells of the islets of Langerhans within the pancreas, impacting the synthesis and secretion of insulin (Johnston et al., 2016; Mangmool et al., 2017). As propranolol is highly lipophilic, it enters the blood–brain barrier, indicating its potential use for anxiety disorders (Steenen et al., 2016). Anecdotally, beta blockers such as propranolol have been used for decades to manage situational anxiety such as stage fright, exam- or interview-related anxiety (Brantigan et al., 1982; Stone et al., 1973).

In light of this, propranolol may hold therapeutic benefit for those with EBAD. In this instance, propranolol may alleviate symptoms relating to autonomic dysregulation and/or hyperarousal, improving the therapeutic outcomes of a child with ASD and EBAD. Similarly, by reducing autonomic dysregulation and hyperarousal, the emotional and behavioural difficulties may also be alleviated. Furthermore, propranolol has been shown to help manage patients with ABIs who may experience EBAD (Chew and Zafonte, 2009; Francisco et al., 2007).

Despite these clinical implications, there remains a dearth in the literature investigating the effectiveness of propranolol in the treatment of anxiety and aggression in ASD. However, published data have shown a significant reduction in aggression in adolescents with ASD (Kuperman and Stewart, 1987), organic brain dysfunction (Greendyke et al., 1986; Schmidt et al., 1995; Williams et al., 1982), and anxiety disorders (Connor and Steingard, 1996; Sweeny et al., 1998).

This report seeks to present a literature review appraising propranolol in the treatment of ASD.

Materials and methods

A systematic, electronic database search for articles was conducted. The databases included PsychINFO (1806 – July Week 5 2017), Embase (1974 – week 31 2017), and Medline (1946 – July Week 4, 2017) via OvidSP. The search criteria were: 'propranolol' OR 'beta blockers' OR 'beta-adrenergic' OR 'β-blockers' OR 'Hemangeol' OR 'Inderal' OR 'Inderal LA' OR 'InnoPran XL' combined with AND 'autism spectrum disorder' OR 'autism' OR 'developmental disorder' OR 'ASD' OR 'autistic spectrum disorder' OR 'autistic' OR 'pervasive developmental disorder' OR 'PDD' or 'Asperger's syndrome' OR 'Asperger's'. No age restrictions were set. Cross-references, including conference abstracts were searched for from identified articles.

Population characteristics

Patients with a primary diagnosis of ASD or Pervasive Developmental Disorder (PDD) were included. Diagnosis was defined as surpassing clinical cut-off points on validated scales and/or assessments, using the International Classification of Diseases (ICD; World Health Organisation, 1992), Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 2013), Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and the Gilliam Asperger's Disorder Scale (GADS; Gilliam, 2001). Multiple versions of these measures, including historical clinical descriptions, were deemed permissible to ensure the review of the literature was all-encompassing.

Intervention

All studies reporting on the use of propranolol in the treatment of ASD were included.

Study design

All published articles including letters, audits, conference abstracts and book chapters were included. Reviews were excluded. To be fully inclusive, single case studies investigating propranolol were included and reported within this review. Articles were rated against eligibility criteria and subsequent consensus by additional researchers within the clinical research team.

Data extraction

Data extracted consisted of: study type, patient demographics, dose, study design, primary outcome measure, results and clinical observations (Table 1). Any study with data relating to pre- and post-administration of propranolol, any clinical observations of propranolol, and longitudinal symptom changes were also included.

Results

Once the strategy outlined above and duplicates were removed, 373 reports were identified. After screening these reports via title and abstract, with the inclusion/exclusion criteria having been implemented, 16 reports remained (Figure 1).

Single-dose clinical trials

Cognitive performance

For six studies, propranolol was administered to enhance cognitive performance. Cognitive performance included verbal problem solving (Beversdorf et al., 2008; Zamzow et al., 2017), semantic and phonological networks (Beversdorf et al., 2011), working memory (Bodner et al., 2012), facial scanning (Zamzow et al., 2014), and conversation reciprocity (Zamzow et al., 2016).

These studies all administered 40 mg of propranolol 60–75 minutes before a task to achieve maximum blood plasma levels. Both Beversdorf et al. (2008) and Zamzow et al. (2017) reported significant improvements in correct anagram latency (e.g. ifrtu = fruit) in the ASD propranolol condition when compared with the ASD placebo condition ($p \leq 0.05$). Similarly, Beversdorf et al. (2011) reported significant improvements for semantic processing, where the ASD propranolol group generated significantly more category-specific words (category fluency task) compared with the ASD placebo group ($p = 0.019$). For phonological processing measured via the letter fluency task, participants named as many words beginning with a given letter, in which a non-significant difference between groups was observed. In contrast, the non-ASD propranolol condition did not see a significant change in either the semantic or phonological networks (category or letter fluency tasks), nor the verbal problem solving task (Beversdorf et al., 2008, 2011).

Moreover, Bodner et al. (2012) investigated the outcomes of propranolol for executive functioning in adults with ASD. Executive functioning was measured via the AX-CPT task (Carter et al., 1998; Cohen et al., 1996) where a target button was to be pressed when they saw a cue letter 'X' that immediately follows a probe letter 'A', and for other stimuli they pressed a non-target button. For both inhibitory control (AY condition) and general attention ability (AX and BY conditions), the number of errors in both the non-ASD propranolol and the ASD propranolol conditions were not influenced. However, for working memory (BX condition), a significant reduction (−11.3%) in the number of errors in the ASD propranolol condition was observed when compared with the ASD placebo group (Bodner et al., 2012). No significant results on working memory for the non-ASD group across all executive functioning domains were obtained (Bodner et al., 2012).

Two reports by Zamzow et al. (2014, 2016) also administered 40 mg of propranolol, with a 60-minute delay to allow for drug metabolism. Participants for the facial scanning investigation were randomised to a propranolol or placebo condition followed by an eye movement monitor to measure facial scanning (Zamzow et al., 2014). Facial scanning was measured via attention given to the eyes, nose and mouth of each stimuli. Both investigations by Zamzow et al. (2014, 2016) utilised a double-blind, counterbalanced, crossover design. Conversation reciprocity was measured using the Conversational Reciprocity Task of the General Social Outcome Measure scale (GSOM CR), focusing on six domains; staying on topic, sharing information, reciprocity, transitions/interruptions, non-verbal communication and eye contact (Zamzow et al., 2016).

Both studies compared an ASD propranolol condition to an ASD placebo condition, with the facial scanning study also having a healthy control comparison. For facial scanning, eye contact did not significantly differ between the ASD propranolol and the ASD placebo conditions. However, a significant reduction in mouth fixation was observed in the ASD propranolol condition when compared with the ASD placebo condition ($p = 0.015$). No significant differences were observed between the non-ASD propranolol and placebo conditions. Total score on the GSOM CR was significantly better in the ASD propranolol condition compared with the ASD placebo condition ($p = 0.03$). Furthermore, improvements in conversation reciprocity were evident for only non-verbal communication; the other five domains did not differ between the ASD propranolol and the ASD placebo condition. Lastly, there was no significant change in self-reported anxiety scores as measured by the Beck Anxiety Inventory and the

Table 1. Demographic and clinical characteristics of included studies.

Study	Participants (n)	Age in years ± SD	Primary diagnosis	β-blocker and dose	Study design	Primary outcome measure	Results	Clinical observations
Single-dose clinical trials (*n* = 8)								
***Cognitive performance* (*n* = 6)**								
Beversdorf et al. (2008)	18 (9 ASD, 89% male; 9 HC, 78% male)	ASD: 29.20 ± 9.90; HC: 23.40 ± 2.20	ADI-R and GADS	Propranolol (40 mg) vs. placebo (N.S.)	Double-blind, counterbalanced, placebo controlled	Successful completions of anagrams	Sig. improvement for anagram completions for propranolol vs. placebo ($p = 0.05$)	Sig. decrease for HR and BP in propranolol group
Beversdorf et al. (2011)	28 (14 ASD, 71% male; 14 HC, 71% male)	ASD: 18.90 ± 2.90, HC: 19.40 ± 2.00	ADI-R	Propranolol (40 mg) vs. placebo (N.S.)	Randomised, double-blind, counterbalanced, crossover, placebo controlled	Average number of words over three trials within each task type (letter, category)	Sig. better performance in category fluency task for propranolol vs. placebo ($p = 0.03$)	Sig. decrease for HR and BP in propranolol group
Bodner et al. (2012)	27 (14 ASD 71% male; 13 HC 69% male)	ASD: 18.90 ± 2.90; HC: 19.20 ± 2.00	DSM-IV ASD and ADI-R; ×7 ASD and ×7 Asperger's	Propranolol (40 mg) vs. placebo (40 mg sugar pill)	Double-blind, counterbalanced, crossover, placebo controlled	Response time to correct letter pair. No. of errors	Sig. improvement in working memory for propranolol vs. placebo ($p < 0.05$); non-sig. improvement for inhibitory control and attention for propranolol vs. placebo ($p > 0.05$)	None reported
Zamzow et al. (2014)	26 (12 ASD, 75% male; 14 HC, 71% male)	ASD: 18.25 ± 2.66; HC: 19.36 ± 2.02	ADI-R	Propranolol (40 mg) vs. placebo (oral capsule)	Double-blind, counterbalanced, crossover, placebo controlled	Changes in areas of interest; absolute mean time spent looking at these AOIs	Sig. decrease in mouth fixation ($p = 0.015$) for propranolol group; non-sig decrease for eye fixation ($p = 0.73$)	None severe (fall in HR in propranolol condition)
Zamzow et al. (2016)	20 ASD (95% male)	21.39 ± 4.55	ADI-R and DSM-IV ASD	Propranolol (40 mg) vs. placebo (oral capsule)	Randomised, double-blind, counterbalanced, crossover, placebo controlled	GSOM CR measure changes in behaviour	Sig. improvement in GSOM CR total score for propranolol group ($p = 0.03$)	None reported
Zamzow et al. (2017)	20 ASD (95% male)	21.39 ± 4.55	ADI-R and DSM-IV ASD	Propranolol (40 mg) vs. placebo (oral capsule)	Randomised, double-blind, counterbalanced, crossover, placebo controlled	No. of anagrams correctly solved and mean latency(s) to correct response. Autonomic activity (HR and BP)	Sig. shorter solution latency for propranolol vs. placebo ($p = 0.02$); Sig. negative linear relationship between propranolol response and HRV	Sig. decrease for systolic BP and HR after propranolol

Table 1. (Continued)

Study	Participants (n)	Age in years ± SD	Primary diagnosis	β-blocker and dose	Study design	Primary outcome measure	Results	Clinical observations
***Neural correlates* (*n* = 2)**								
Narayanan et al. (2010)	10 ASD (80% male)	24.30 ± 4.37	ADI-R and GADS	Propranolol (40 mg) vs. placebo (N.S.) vs. nadolol (50 mg)	Double-blind, counterbalanced, placebo controlled study	Completion of phonological task	Sig. greater functional connectivity between LIFG and LFG ($p < 0.05$)	Sig. decrease for HR and BP in a similar manner from baseline to pre-fMRI for propranolol and nadolol
Hegarty et al. (2017)	30 (15 ASD 85% male) (15 HC 85% male)	ASD: 22.21 ± 4.16; HC: 22.86 ± 2.68	ADI-R	Propranolol (40 mg) vs. nadolol (50 mg) vs. placebo (N.S.)	Blinded, counterbalanced, matched control, placebo controlled	Changes in functional connectivity for dMPFC, MTL and DMN	Sig. lower FC for propranolol vs. placebo ($p = 0.02$) for the dMPFC subnetwork; sig. increase in FC for MTL subnetwork ($p = 0.017$)	Sig. decrease for HR for all groups; greater decrease for nadolol; non-sig. changes for anxiety
Behavioural case series (*n* = 5)								
Knabe and Bovier (1992)	2 (100% male)	18 and 30	'Autistic patient' (assessment not specified)	Oxprenolol (80 mg), naltrexone (1.25 mg/kg); propranolol (320 mg), naltrexone (100 mg)	Two cases	Reduction in aggressive behaviours and SIBs	Immediate reduction for aggressive behaviours and SIBs respectively for propranolol	None reported
Ratey et al. (1987)	8 (88% male)	32.00 ± 8.06	×7 Diagnosis of infantile autism; ×1 met National Society for Autistic Children criteria	Propranolol (360 mg/day, 160 mg/day, 100 mg/day, 180 mg/day); nadolol (120 mg/day)	Eight cases	Changes in SIBs, and aggressive behaviour	Reduction in aggression and SIBs for both propranolol and nadolol cases	Hypotension, medication was changed if needed to; no-one dropped out
Lyskowski et al. (2009)	5 (100% male)	26, 20 and 21	Multiple diagnoses (Manual not specified)	Quetiapine (300 mg), lithium (300 mg), sodium valproate (300–500 mg), propranolol (20 mg)	Five cases	Bi-weekly frequency of restraints, seclusion and harm to self or others	Reduction in aggression and SIBs for propranolol group, therefore, able to engage in DBT	Jaundiced and confusion, both thought to be in response to lithium
Santosh et al. (2017)	5 (100% male)	16.25 ± 2.24	ICD-10 diagnosis of ASD	Propranolol (40 mg)	Five patients, including one case report	Changes in EBAD symptoms and physiological changes in intra-beat interval and electro-dermal activity recorded by a wearable wristband device	Sig. reductions in EBAD symptoms, alongside sig. reductions in maximum heart rate and average heart rate frequencies; they showed sig. decreases in intra-beat interval and electro dermal activity	None reported

(Continued)

Table 1. (Continued)

Study	Participants (n)	Age in years ± SD	Primary diagnosis	β-blocker and dose	Study design	Primary outcome measure	Results	Clinical observations
Sagar-Ouriaghli et al. (2017)	23 (65% male)	15.00 ± 2.65	ICD-10	Propranolol (44.67 mg ± 22.31 mg)	Observational design	POTR and CGI completed by clinicians as part of routine clinical practice	Sig. reduction in anxiety, aggression and explosive rage; sig. improvement in CGI scores	Increased appetite
Behavioural case reports (*n* = 3)								
Connor (1994)	1 (male)	11	DSM-III-R diagnoses of PDD, mental retardation and pica	Propranolol (80 mg/day), nadolol (80 mg/day)	Open-trial case study	CAPS score; aberrant behaviour checklist; SIBs, pica, side effects.	Non-sig difference in CAPS score for propranolol. Sig. reduction in SIBs for nadolol	Propranolol withheld due to hypotension (80 mg+); mild transient insomnia, sedation, nausea, and diarrhoea; nadolol, mild sedation
Agrawal (2014)	1 (male)	13	'Severe autism' (Manual not specified)	Propranolol (20 mg)	Single-case study	Diary measuring changes in hypersexual behaviours	Frequency of hypersexual decreased at home and school	None reported
Luiselli et al. (2000)	1 (male)	12	'Diagnosis of autistic disorder' (manual not specified)	Sertraline, 16 weeks; (2) Clonazepam, 1 week; (3) Propranolol, 9 weeks; (4) Clomipramine, 51 weeks	Single-case experimental design	Frequency of aggressive episodes and emergency interventions	Av. aggressive episodes: baseline, 3.0/day; sertraline, 3.2/day; clonazepam, 4.0/day; propranolol, 3.1/day; clomipramine, 0.9/day	Propranolol was discontinued due to hypotension and bradycardia

ADI-R: autism diagnostic interview revised; AOIs: areas of interest; ASD: autism spectrum disorder; Av.: average; BP: blood pressure; CAPS: Child Attention Problems Scale; CGI: Clinical Global Impression ; DBT: dialectical behavioural therapy; DMN: default mode network; dMPFC: dorsal medial prefrontal cortex; DSM-III-R: Diagnostic and Statistical Manual III-revised; DSM-IV: Diagnostic Statistical Manual IV; EBAD: emotional behavioural and autonomic dysregulation; FC: functional connectivity; fMRI: functional magnetic resonance imaging; GADS: Gilliam Asperger's Disorder Scale; GSOM CR: Conversational Reciprocity task of the General Social Outcome Measure; HC: healthy controls; HR: heart rate; HRV: heart rate variability; ICD-10: International Classification of Diseases-10; LFG: left fusiform gyrus; LIFG: left inferior frontal cortex; MTL: medial temporal lobe; Non-sig: non-significant; N.S.: not specified; PDD: pervasive developmental disorder; POTR: profile of treatment response; SIBs: self-injurious behaviours; SD: standard deviation; Sig.: significant.

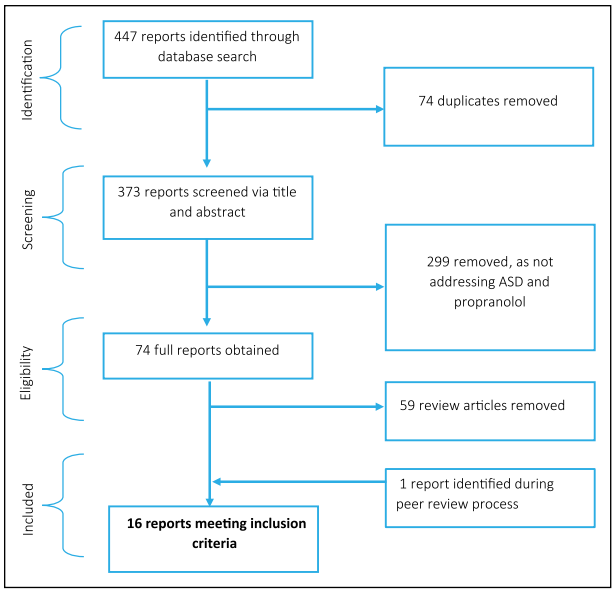

Figure 1. PRISMA flow chart summarising study selection process.
PRISMA: Preferred reporting items for systematic reviews and meta-analyses; ASD: Autism spectrum disorder.

Spence Children's Anxiety Scale after the administration of propranolol (Zamzow et al., 2016), which was also replicated by Zamzow et al. (2017) at a later date.

Lastly, Zamzow et al. (2017) conducted further analyses into autonomic activity. Prior to each testing session baseline electrocardiography (ECG), required to calculate heart rate variability (HRV), and skin conductance were measured. HRV was calculated from either inter-beat intervals, R–R intervals (RMSSD), or the proportion of successive R–R intervals that differ by more than 50 ms (pNN50). A significant negative linear relationship between response rate to propranolol for mean solution latency and mean baseline RMSSD was observed ($p = 0.04$, $R^2 = 0.35$). This significant negative relationship remained between propranolol response for solution latency and mean baseline pNN50 ($p = 0.04$, $R^2 = 0.35$). Indeed, this indicates that those with lower HRV may experience the largest benefits from propranolol for anagram solution latency in comparison with individuals with high HRV, acting as a biomarker for treatment response.

Neural correlates

Two studies by Hegarty et al. (2017) and Narayanan et al. (2010) investigated the impact of propranolol on functional connectivity, with Hegarty et al. (2017) having specificity to the dorsal medial prefrontal cortex, medial temporal lobe and the default mode network. Both these reports compared propranolol administration with a 50 mg dose of nadolol in adult ASD populations, with Hegarty et al. (2017) utilising a non-ASD control group. Nadolol is similar to propranolol as it is also a non-selective β-blocker, inhibiting beta 1 (b1) and beta 2 (b2)-adrenergic receptors (Heel et al., 1980; Mehvar and Brocks, 2001). Contrasting to propranolol, nadolol is hydrophilic (Meier, 1982), and does not operate centrally, providing only peripheral blockade (Beversdorf et al., 2002). Therefore, by making comparisons between propranolol and nadolol helped to control for confounding effects of reduced heart rate and systolic blood pressure when taking functional magnetic resonance imaging (fMRI) readings.

Narayanan et al. (2010) administered propranolol (40 mg), nadolol (50 mg) or a placebo to adults with ASD, to observe functional connectivity. Functional connectivity was assessed within an fMRI scanner whereby participants identified which word from a list rhymed with a cue word (Narayanan et al., 2010). The ASD propranolol condition revealed a significant increase in greater functional connectivity between the left fusiform gyrus and left inferior frontal cortex ($p = 0.004$) compared with those in the ASD nadolol condition. Hegarty et al. (2017) reported that functional connectivity significantly decreased in the dorsal medial prefrontal cortex (dMPFC; $p = 0.020$), and a significant increase in the medial temporal lobe (MTL) subnetwork ($p = 0.017$), when compared with the ASD placebo condition. Finally, whole brain bilateral default mode network levels did not differ significantly across all groups (Hegarty et al., 2017).

Behavioural case series and case reports

To date, much of the literature surrounding propranolol for ASD has been prescribed to help with the management of aggression and self-injurious behaviours (SIBs). Three case series and two case reports sought to treat aggression and SIBs using propranolol in individual case studies (Connor, 1994; Knabe and Bovier, 1992; Luiselli et al., 2000; Lyskowski et al., 2009; Ratey et al., 1987). One trial explored the efficacy of propranolol in managing hypersexual behaviours (Agrawal, 2014). Another report focused on HRV recorded by wearable devices in order to manage EBAD (Santosh et al., 2017), with the final study focusing on the effectiveness of propranolol within a clinical sample as measured by a treatment response scale from clinicians (Sagar-Ouriaghli et al., 2017). No clinical trials or experimental designs were identified.

Case series

From the case series, there was only one report that sought to treat aggression and SIBs with solely propranolol (Ratey et al., 1987). This article discusses the efficacy of propranolol in managing impulsive, aggressive, and SIBs across seven adults diagnosed with autism. Across these seven cases, the propranolol dose ranged from 100 mg to 360 mg a day all leading to positive therapeutic effects, and a significant reduction in aggression and SIBs. One case saw a 77% decrease in target behaviours, consisting of head banging, knee biting and clothes ripping over a 10-month period (Ratey et al., 1987). The mean duration of treatment lasted 14.2 months. Other benefits reported by staff included a reduction in impulsive stealing, higher tolerance for social and interpersonal interactions, increased attention and improved speech patterns (Ratey et al., 1987). Furthermore, from the Ratey et al. (1987) case series, two participants received nadolol. The first case received propranolol (160 mg/day) preventing incidents of aggression, self-abuse, increase sociability and improved speech, yet needed to be withdrawn due to hypotension. Subsequently, they were switched to 120 mg of nadolol a day for dosing conveniences with no changes in the treated target

behaviours. The second case received 120 mg of nadolol for aggression and SIBs, and saw immediate decreases in hyperactivity, head banging, and was more sociable and closer to others.

Three other case series were identified with a diagnosis of autism, PDD or mild intellectual disability (Knabe and Bovier, 1992; Lyskowski et al., 2009). Two of the three cases were treated with propranolol alongside other medications in the treatment of aggression and SIBs. The third case received oxprenolol as opposed to propranolol (Knabe and Bovier, 1992), another non-selective lipophilic β-blocker with affinity for both b1 and b2 receptors, providing both central and peripheral blockade (Frishman and Silverman, 1979; Kendall and John, 1983). Oxprenolol was prescribed alongside other medications in the treatment of aggression and SIBs. The first propranolol case received 20 mg of propranolol combined with quetiapine (300 mg), lithium (300 mg), and sodium valproate (2500 mg) (Lyskowski et al., 2009). The second case received 320 mg of propranolol in conjunction with naltrexone (100 mg) and clopenthixol-decanoate (300 mg) (Knabe and Bovier, 1992). Improvements were reported for both cases, including a greater ability to manage stress. Indeed, this enabled them to engage in a dialectical behavioural therapy programme (Lyskowski et al., 2009), and exhibited increased sociability because of their reduced SIBs (Knabe and Bovier, 1992). The final case receiving the oxprenolol combination saw all SIBs cease for 2 years (Knabe and Bovier, 1992).

Two other reports focus on specifically investigating propranolol in the management of EBAD and assess the clinical effectiveness in the management of anxiety and explosive rage in ASD (Sagar-Ouriaghli et al., 2017; Santosh et al., 2017). Both these reports utilised a mean dose of around 40 mg of propranolol, with the Sagar-Ouriaghli et al. (2017) study reporting a mean dose of 44.67 mg, ranging from 7.5 mg to 80 mg. This study reported a significant reduction in anxiety, aggression and explosive rage at follow up (24 ± 12.71 months). In addition to these findings, Clinical Global Impression scores as part of the Profile of Treatment Response Scale (POTR; Santosh et al., 2017) highlighted that 90% of the sample showed a good or excellent response to propranolol treatment. Furthermore, a mean Therapeutic Efficacy Index score of 3.16 highlighted that the majority of this patient group experienced a moderate-marked therapeutic improvement without any or non-significant side-effects. Only one individual had an Efficacy Index of 0.75, denoting that the side effects outweighed the therapeutic benefits, despite there being a moderate therapeutic improvement of symptoms.

In the recent Santosh et al. (2017) report, both symptoms and biometric biomarkers of EBAD – intra-beat interval (IBI) and electro-dermal activity (EDA) captured via a wearable wristband, were evaluated pre- and post- administration of propranolol. Propranolol significantly reduced EBAD symptoms and also reduced the maximum heart rate and average heart rate at a mean of 122 days follow up. Furthermore, a significant reduction in both the IBI and EDA was reported in one adolescent with ASD (aged 17) at follow up after receiving a 40 mg propranolol dose (Santosh et al., 2017).

Case reports

From the remaining case reports, two sought to treat aggression and SIBs (Connor, 1994; Luiselli et al., 2000) with one report focusing on the behavioural management of hypersexual behaviours (Agrawal, 2014).

Connor (1994) separately trialled both propranolol and nadolol to target irritability, aggression, SIBs, inattention, impulsivity and motor over-activity in an 11-year-old boy diagnosed with PDD, mental retardation and pica. After 3 months of baseline readings, propranolol was introduced for 4 months starting with a dose of 10 mg, titrated with a 10 mg increase every 3 days, reaching 80 mg a day. Across 18 weeks, propranolol had to be withheld 11 times due to the patient's pulse and/or blood pressure falling below safety thresholds. Over-activity and inattention remained constant, deeming propranolol ineffective (Connor, 1994). Due to lack of improvement, propranolol was stopped and nadolol was introduced 5 days later, starting at 20 mg, titrated with a 20 mg increase every 5 days, reaching 80 mg per day. Nadolol saw a significant decrease in scores for the Child Attention Problems Scale and in the frequency of SIBs, with an overall improvement in irritability, aggression, SIBs, inattention and over-activity ranging from 48–78% (Connor, 1994). These improvements were maintained at 5-month follow up, indicating nadolol was better tolerated than propranolol.

Lastly, Luiselli et al. (2000) conducted a 77-week open trial utilising sertraline, clonazepam, propranolol and clomipramine, respectively. Target behaviours consisted of aggressive episodes defined as biting, scratching, hitting, pinching, pulling hair or grabbing clothing of another person, in a 12-year-old boy diagnosed with ASD. Sertraline was introduced first (12.5 mg/day) for 16 weeks, noting a gradual decrease in aggressive episodes, before reverting to an increase, averaging 3.2 aggressive episodes per day. Once sertraline was discontinued after the 16 weeks, clonazepam was introduced (0.5 mg/day) for 1 week, resulting in an increase in average daily aggressive episodes. As the average daily aggressive episodes increased to 4.0 episodes per day, clonazepam was subsequently stopped. This count of 4.0 episodes remained constant for the 9-week propranolol phase (10 mg titrated to 40 mg), despite a trend of decreasing episodes in the last 2 weeks of this phase. Similarly, due to a poor improvement in aggressive episodes and the patient's experience of hypotension and bradycardia, propranolol was stopped. Finally, clomipramine (25 mg/day) was introduced for 8 weeks, before being increased to 50 mg and then 75 mg per day for a further 43 weeks. Clomipramine saw an immediate and stable reduction in aggressive episodes falling to 0.9 episodes per day, with aggressive episodes remaining absent for 28% of these days (Luiselli et al., 2000).

Agrawal's (2014) case report sought to treat a 13-year-old boy with ASD who exhibited, on average, 70 major hypersexual behaviours a day. Incidents were recorded by his mother and school staff in a diary. Initially, propranolol was administered twice a day (10 mg × 2) with the intention to optimise the dose. After 2 weeks, the 20 mg dose reduced the average number of incidents a week from 70 to 20. Furthermore, 3 months after the initial 2 weeks' propranolol treatment phase, only one incident occurred in a 2-month period. After the 3-month treatment phase, a situation prevented the individual from taking propranolol for 2 weeks, whereby his hypersexual behaviours returned to almost 50 incidents per week. Propranolol was resumed and hypersexual behaviours decreased again. Lastly, treatment continued for 1 year without any notable side effects.

Current clinical investigations

Based on their previous findings of improved cognitive functioning, Beversdorf and colleagues are currently investigating propranolol as a treatment for the core features of ASD (https://clinicaltrials.gov/show/NCT02871349). The specific aim of Beversdorf and colleagues' ongoing study being conducted is to examine the effects of serial doses of propranolol on social interaction, language tasks, anxiety, adaptive behaviours, and global function in high-functioning adults and adolescents with autism in a double-blinded, placebo-controlled trial (DBPCT). They will also examine whether response to treatment can be predicted by markers of functional connectivity or autonomic functioning, such as skin conductance, HRV, and the pupillary light reflex (PLR), and whether anxiety can predict treatment response. Based on previous literature, they hypothesise that social functioning and language abilities will benefit from serial doses of propranolol, and that those with the greatest degree of autonomic dysregulation, or the lowest functional connectivity, will demonstrate the greatest benefit from the drug.

Supplementary literature

As there were no propranolol trials of good quality available in ASD, we specifically looked for randomised controlled trials in acquired brain injury because of the overlap of symptoms such as social communication problems and EBAD. Two randomised controlled trials (RCTs; Brooke et al., 1992; Greendyke et al., 1986) were identified within a Cochrane review (Fleminger et al., 2006) supporting the use of propranolol to manage symptoms of aggression in those with acquired brain injury (ABI). The Brook et al. (1992) RCT utilised propranolol to manage agitation in 21 adults with ABIs. Agitated behaviour was measured using the Overt Aggression Scale (Yudofsky et al., 1986), use of restraints and the use of supplementary medication to assist with agitation and/or sedation. Those in the propranolol arm (n=11) received 60 mg a day, increased by an additional 60 mg every third day until agitation curtailed or side effects became present. A ceiling of 420 mg was maintained throughout the study. After the initial 3-week period, drug dosages were tapered over the following 2 weeks. Indeed, a significant reduction in the average maximum intensity of agitated episodes ($p < 0.05$) across an 8-week period was observed. Despite this, the frequency of agitated episodes did not significantly improve. The second RCT by Greendyke et al. (1986) provided a long-acting dose of propranolol, starting at 80 mg a day, upped by an additional 80 mg every 3–4 days, until a ceiling of 520 mg was maintained. After this titration period, 520 mg/day was administered for a course of 11 weeks before being tapered to 0 mg/day. Similarly, a significant reduction in attempted and completed assaults was observed, falling from 88 to 52 assaults across two 11-week intervals in 10 patients. This provides further support for the use of propranolol, as both ABI and ASD present with neurological difficulties (Sparks et al., 2002).

Discussion

From the 16 articles identified, propranolol dosages ranged from 7.5 mg to 360 mg per day across a range of patients. All studies had a range of outcome measures for those diagnosed with ASD, including a focus on cognitive enhancement, management of social behaviours, EBAD, SIBs, and aggression.

Summary of evidence

Across multiple domains, propranolol had significant benefits in the treatment of adults and children diagnosed with ASD. Propranolol improved cognitive performance, with individuals with ASD demonstrating an improvement in verbal problem solving (Beversdorf et al., 2008; Zamzow et al., 2017), semantic processing (Beversdorf et al., 2011) and working memory (Bodner et al., 2012). No changes in cognitive performance for individuals without ASD were reported (Beversdorf et al., 2008, 2011). Additionally, propranolol exhibited greater functional connectivity in individuals with ASD (Hegarty et al., 2017; Narayanan et al., 2010). Not only does this provide evidence for the ability of propranolol to improve functional connectivity in those with ASD, but also that central and peripheral blockade is more effective than just peripheral blockade as seen by nadolol (Hegarty et al., 2017). It is important to note that a non-significant difference for functional connectivity between placebo and propranolol conditions can be attributed to other hemodynamic factors, such as differences in blood pressure, confounding the effects on blood-oxygen-level-dependent responses during fMRI sessions (Narayanan et al., 2010). Moreover, propranolol decreased functional connectivity in various subnetworks where high baseline functional connectivity was observed. Conversely, for those with low baseline functional connectivity, functional connectivity in these subnetworks increased after the introduction of propranolol, irrespective of diagnostic group (Hegarty et al., 2017). These differences suggest that propranolol, and other beta-adrenergic antagonists may have a greater role in maintaining appropriate patterns of functional connectivity, allowing for more efficient integration of functional networks (Hegarty et al., 2017). These findings also highlight the potential for propranolol to support cognitive processing. Indeed, by modulating noradrenaline, greater associative processing and integration of subnetworks may be achieved. Subsequently, potential improvements in attention-shifting, sensory processing, language communication, and the processing of social information could be observed in those with ASD (Hegarty et al., 2017).

Furthermore, propranolol reduced mouth fixation, improving facial scanning at a global level (Zamzow et al., 2014). Although, non-significant findings were reported when investigating the efficacy of single-dose propranolol treatment for eye contact, this may be attributable to the sample used. The majority of subjects fulfilling diagnostic criteria for ASD were high functioning, suggesting that scores for eye contact may have already been at a ceiling prior to the administration of propranolol. Therefore, none or only marginal improvements would be attained from post administration of propranolol leading to non-significant results when compared with controls. Moreover, non-verbal communication improvements (Zamzow et al., 2016) and reductions in hypersexual behaviours (Agrawal, 2014) were also observed. These improvements were reported in studies using a 40 mg dose of propranolol, with just one study utilising a low dose of 20 mg (Agrawal, 2014). However, it may be noteworthy to consider that for this case, the hypersexual behaviours did not decrease while the patient was alone, but the patient was able to manage behaviours more appropriately in the presence of others. This may

indicate an improved ability to understand and interpret social contexts, rather than a reduction in hypersexual behaviours. Indeed, social cues and social situations are a challenge for those with ASD, and these findings highlight potential clinical implications for propranolol.

In light of this, both studies by Sagar-Ouriaghli et al. (2017) and Santosh et al. (2017) highlight again that on average, a 40 mg dose is suitable for children and adolescents in managing symptoms associated with ASD and EBAD. Furthermore, Santosh et al. (2017) and Zamzow et al. (2017) provide supporting evidence for the use of wearable technologies in measuring biomarkers such as HRV and skin conductance in order to identify treatment responders and monitoring the impact of propranolol on therapeutic outcomes. Alongside these benefits, propranolol significantly helped manage SIBs and aggressive outbursts in those with ASD (Knabe and Bovier, 1992; Lyskowski et al., 2009; Ratey et al., 1987). Two cases reported no significant improvement when using propranolol (Connor, 1994; Luiselli et al., 2000). One case was required to change propranolol due to hypotension and bradycardia despite a decreasing trend in aggressive behaviours (Luiselli et al., 2000). Across these cases, dosing ranged from 7.5 mg–360 mg, indicating a higher dose may be required for SIBs and aggression, in comparison with cognitive performance (20 mg–40 mg).

In summary, these results and a subsequent overview by Fleminger et al. (2006) conclude that β-blockers have the best evidence for the management of such symptoms and that propranolol improves impulse control and subsequent violence associated with brain dysfunction of diverse aetiologies.

Limitations

The limitations of the published longitudinal clinical trials are that they are open-label naturalistic studies and hence prone to bias, and that standardized assessments for ASD, EBAD and autonomic dysfunction have not been used uniformly in all studies. The experimental studies have predominantly focused on ASD with relatively normal cognitive ability and the longitudinal clinical studies showing improvements in EBAD contain a mix of patients with different levels of cognitive ability and hence one cannot be certain that findings apply across the spectrum of cognitive ability in those with ASD. Varying doses of propranolol have been used in the numerous studies questioning the reliability of such results, and whether any additional factors may have contributed to significant findings. Having identified dosage issues, one must highlight the variation in an individual's metabolism of propranolol. Considering propranolol is highly protein-bound, resulting in drug–drug interactions (Riddle et al., 1999), appropriate doses need to be tailored, particularly for polypharmacy approaches. Furthermore, all publications on aggression and SIBs are case reports with one case report on the management of hypersexual behaviours. It is important to note here that all apart from the reports by Sagar-Ouriaghli et al. (2017) and Santosh et al. (2017) lack the inclusion of quantitative measures. Some studies cannot account for medication cross-over effects (Luiselli et al., 2000), and fail to identify the medication responsible for beneficial effects when a polypharmacy approach is adopted (Lyskowski et al., 2009). Additionally, the single-administration studies contain tasks that are complex in nature, and thus low-functioning individuals with ASD were not recruited. Where complex patients have been included, propranolol still seems to hold promise with reduction in aggression, improvements in Clinical Global Impression score and reduction in IBI and EDA (Sagar-Ouriaghli et al., 2017; Santosh et al., 2017). However, propranolol for low-functioning individuals with ASD remains fairly unexplored, as this population is of great interest. Improvements in anxiety symptomology appears to be mixed, with Sagar-Ouriaghli et al. (2017) and Santosh et al. (2017) observing an improvement in low-functioning individuals with ASD, which contrasts to the findings by Zamzow et al. (2016, 2017), whereby self-reported anxiety scores do not change. Indeed, Zamzow et al. (2016) highlight that self-report measures for anxiety may not be appropriate due to individuals with ASD lacking introspection, and thus parent or clinician reports should be used. It is also possible that single doses of propranolol may not produce the clinical benefit on anxiety being reported in the longitudinal clinical studies.

Although case reports containing one patient were included to enhance the scope of this review, we are unable to delineate if such improvements are a result of propranolol or not, due to lacking in statistical power (Dybå et al., 2006). Moreover, all validated scales for autism were included, resulting in the inclusion of studies that have not specified the method or used clinically relevant methods to identify patients with ASD (Agrawal, 2014; Knabe and Bovier, 1992; Luiselli et al., 2000; Lyskowksi et al., 2009; Ratey et al., 1987). Therefore, it is hard to ensure that these findings are generalisable to those fulfilling ASD criteria, as defined by the ADI-R, GADS, DSM or ICD. However, taking this into consideration, 11 of the 16 articles included in the review did have DSM/ICD diagnoses or utilised validated instrument such as the ADI-R or GADS (Beversdorf et al., 2008, 2011; Bodner et al., 2012; Connor, 1994; Hegarty et al., 2017; Narayanan et al., 2010; Sagar-Ouriaghli et al., 2017; Santosh et al., 2017; Zamzow et al., 2014, 2016, 2017). Lastly, although any queries regarding study eligibility were resolved by consensus with additional researchers, absolute selection objectivity cannot be ensured (Liberati et al., 2009).

Future directions

Based on the review, it appears that propranolol may have many different benefits in ASD. Considering the majority of the literature has utilised case studies to evaluate the efficacy of propranolol for aggression and SIBs, future DBPCTs seeking to replicate these results would be a good starting point to further validate and support this finding. There is an urgent need to conduct large longitudinal DBPCTs of propranolol, where standardised assessments are used for ASD and EBAD, and the trials should involve patients with the whole range of cognitive ability. Measures of autonomic function using wearable sensor-based assessments and MRI-based functional connectivity measures may help identify biomarkers that may predict propranolol responders. Also, age of ASD subjects may play a role in improvement and studies should therefore also focus on children, as it is possible that age at which propranolol is initiated may have an impact on how much improvement is possible. Other β-blockers that have some central action should also be investigated in this patient population to identify whether they show similar or better therapeutic response profiles.

Conclusion

The evidence highlighted provides evidence that the use of propranolol may result in significant improvements in EBAD, the symptomatology of ASD, with a focus on cognitive performance and neural correlates and the management of behaviour, predominantly for aggression and SIBs. Single-dose studies of propranolol in ASD focusing on the social communication deficits suggests that propranolol improves (a) abnormalities in facial scanning, by reducing the increased mouth fixation (Zamzow et al., 2014); (b) conversational reciprocity and nonverbal communication (Zamzow et al., 2016); (c) functional connectivity and alters coordinated functional activation in the brain, as measured by default mode network (Hegarty et al., 2017); and (d) verbal problem solving, especially in those with significant baseline autonomic arousal and anxiety (Zamzow et al., 2017b). Longitudinal clinical studies have shown that propranolol improves EBAD in ASD (Sagar-Ouriaghli et al., 2017; Santosh et al., 2017) and case studies report an improvement in aggression and SIB.

More evidence to evaluate the effectiveness of propranolol is warranted, particularly through randomised controlled trials. For instance, Beversdorf and colleagues are in the process of conducting a DBPCT for propranolol in ASD which hopes to provide greater clarity in understanding the effects on social interaction, language tasks, anxiety, and global functioning, and autonomic dysregulation via monitoring skin conductance, HRV and the PLR.

Propranolol may be useful in those with greater physiological anxiety through its anxiolytic effect via the autonomic nervous system (Santosh et al., 2017). This may be relevant for those with EBAD helping to combat symptoms of physiological arousal and behaviour dysregulation in ASD (Sagar-Ouriaghli et al., 2017; Santosh et al., 2017; Vasa et al., 2016). For such cases, wearable sensor technologies can be used as a non-invasive method to measure real-time heart rate and electro-dermal activity to screen for autonomic dysregulation, informing suitable treatment options such as propranolol (Santosh et al., 2017).

When utilising propranolol within this patient group it is important to consider that propranolol can impact the synthesis and secretion of insulin, leading to a greater risk of developing diabetes and other metabolic syndromes (Bangalore et al., 2007; Johnston et al., 2016). This is important to consider for complex psychiatric cases where propranolol may be prescribed in conjunction with drugs for psychosis such as risperidone or olanzapine as they are also associated with greater risk of diabetes and metabolic syndromes (Smith et al., 2008).

In summary, wearable sensor technology can be coupled with rating scales to assist in the detection of EBAD, and the evidence suggests that propranolol can be considered as a viable treatment option for complex symptoms in patients with ASD. Hopefully, the ongoing DBPCT of propranolol on ASD should help answer many of the unanswered questions about the true effectiveness of propranolol in managing the core symptoms of ASD as well as EBAD associated with ASD.

Declaration of conflicting interests

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