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RESEARCH ARTICLE

The challenge of detecting adverse events in adults with autism spectrum disorder who have intellectual disability

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Abstract

Adults with autism spectrum disorder (ASD) and associated intellectual disability (ID) take a high number of different psychotropic drugs simultaneously. Nowadays, little is known about this multidrug pattern efficacy and safety. The present study has endeavored to fill this gap creating a local pharmacovigilance system. A 36-month, retrospective and prospective, observational, and multicenter pharmacovigilance study was carried out in adults with ASD and ID ($n = 83$). Information regarding ongoing medications (polypharmacy: taking simultaneously >4 drugs; safety profile: adverse events' number, adverse drug reactions' number, and affected system; and observed-to-expected [O/E] ratio using the summary of product characteristics), and current diagnoses were recorded. A median of four ongoing medications per participant was registered, half of the sample was under polypharmacy regimen. Regarding all ongoing medications, 50% were antipsychotic drugs, and 47% of participants had >1 antipsychotic prescribed. In contrast, only 64 adverse events were identified from electronic health records, mostly due to risperidone. Half of them were related either to nervous or metabolic systems, and almost a third were not previously described in the corresponding drug summary of products characteristics. Extrapyramidalism, gynecomastia, hypercholesterolemia, and urinary retention were some AEs that occurred more frequently than expected (O/E ratio > 6 times) according to our data. The highest O/E ratio scores (>120 times) were for hypercholesterolemia and rhabdomyolysis caused by valproic acid. According to the number of adverse events and adverse drug reactions reported in electronic health records locally and nationally by clinicians, we need to increase awareness about medications safety.

Lay Summary

A 36-month study in adults with autism, ID, and polypharmacy (>4 drugs) was done to investigate drug safety on everyone. A median of four medications per person was registered, half were antipsychotic drugs, and 47% of participants had >1 antipsychotic medication simultaneously. Only 64 adverse events were identified from electronic health records, mostly due to risperidone. Half of them were related to nervous or metabolic systems and a third were not previously described in the drug information sheet.

KEYWORDS
adverse events, autism spectrum disorder, intellectual disability, pharmacovigilance

Pura Ballester and Cristina Espadas contributed equally to this study.

INTRODUCTION

Autism spectrum disorder (ASD) as a lifelong neurodevelopmental condition, displays a high comorbidity burden. In a large study carried out in the United States, 15% of participants apart from ASD had other two diagnosis such as anxiety, depression, aggressive behavior, epilepsy, intellectual disability (ID), or attention deficit and hyperactivity disorder (Houghton et al., 2017). These simultaneous comorbid conditions lead to a population that uses psychotropic medication, singly or on a polypharmacy basis. Several antipsychotic drugs are used to treat aberrant behaviors (Sharma et al., 2018), combined either with antidepressants or anxiolytics for mood fluctuations (Aman et al., 2008; Jobski et al., 2017), and/or antiepileptics for epilepsy or relapse control (Nadeau et al., 2011; Relia & Ekambaram, 2018). Furthermore, the average of ongoing medications tends to increase along the autistic life span from two to five or more simultaneous prescriptions (Charlesworth et al., 2015). Having in mind that drug doses are established in clinical trials where participants only have one disease and take the drug under study, conclusions drawn from them may not be extended to real world patients who take multiple medications simultaneously (Davies & O'mahony, 2015; Storebø et al., 2018).

Thus, despite the scarce information about the effectiveness or suitability of several active ingredients in people with ASD (Vereenooghe et al., 2018), up to 75% of them are under a pharmacological treatment (Jobski et al., 2017), and 35% are under a psychotropic polypharmacy, taking more than four medications simultaneously (Spencer et al., 2013a). Several studies focused on other mental health conditions linked antipsychotic medication with a high risk of suffering serious adverse events (AEs), such as seizures, rhabdomyolysis, or neuroleptic malignant syndrome (Rani et al., 2011; Sheehan et al., 2017; Star et al., 2012). Likewise, antipsychotics may affect the metabolic system functioning, causing weight gain, diabetes mellitus, or hyperprolactinemia (Almandil et al., 2013; Almandil & Wong, 2011), or induce movement disorders, such as tardive dyskinesia, tremor, or dystonia (Fleischhaker et al., 2006). Even though those AEs were not described in studies with participants with ASD, they should be expected in a similar prevalence in this population, and we might be underestimating them. Taking several medications simultaneously can increase hospital visits, increase AEs appearance which foster inappropriate prescribing (Maher et al., 2014; Oscanoa et al., 2017), or AEs may be misinterpreted as they can mimic autism comorbid conditions (Ji & Findling, 2015). As a result of polypharmacy, some patients may suffer AEs and therefore a prescribing cascade (Ponte et al., 2017). All mentioned contributes to an increased risk of fragility, premature aging, and mortality (Miot et al., 2019).

Despite of the importance, clinicians have little engagement with drug AEs monitoring programs due to their overwork, lack of education, and awareness provided by healthcare systems (Cerruti et al., 2016; Reumerman et al., 2018). Thus, pharmacovigilance is still an aspect, which is scarcely explored in the typically developing population, even less in participants with ASD without ID (Fung et al., 2016), or with ID present in up to 68% of participants with ASD (Yeargin-Allsopp et al., 2003). This population is especially vulnerable, as they are not capable of developing a consistent oral language that allows clinical information exchange, which makes difficult to monitor potential drug side effects. The general aim of this study was to explore the safety of regular prescriptions in adults with ASD and ID. Special emphasis was put in identifying adverse effects, due to the intake of multiple drugs simultaneously, through a monitoring data system based on routine medical records. This system may also help to analyze the reporting rates of those AEs to the National Pharmacovigilance System, and their classification.

METHOD

Ethics

This study was approved by the Ethics Committee, carried out in accordance with the requirements expressed in the Declaration of Helsinki, the good practices guidelines by the International Conference of Harmonization, and the Spanish ministerial order SAS/3470/2009 about observational studies. All patients, and/or legal representatives, included in the study have read the patient information form and signed the informed consent. After that moment, all data were anonymized when entered in the database.

Study design and population

A 36-month, observational, retrospective, and prospective, non-interventional, and the multicentric study was conducted in all residential facilities for autistic adults that belong to Alicante Health Department - General Hospital (Alicante, Spain). Data for this study came from a larger study previously published developed at all four residential facilities for autistic adults that belong to our health area (Espadas et al., 2020). These four facilities usually assist around 145 participants who were prescreened, 124 were potential candidates, and after considering inclusion and exclusion criteria 83 adults were finally included (Figure 1). The population included were adults with ASD and ID, living in the four residential facilities, who during the study continued with their routines, ongoing medications, and usual healthcare.

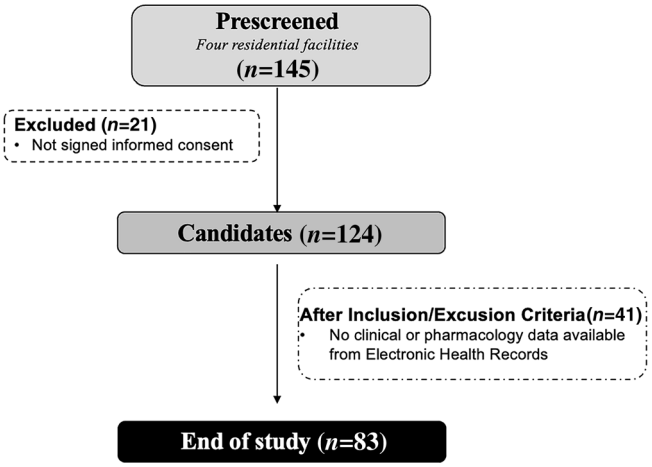

FIGURE 1 Flow chart that illustrates participants' recruitment

Their information was collected from local electronic health records (EHR). Polypharmacy was defined as the intake of ≥4 prescribed drugs simultaneously (Jyrkkä et al., 2009).

To carry out the study, the following inclusion criteria were followed: (a) ASD diagnosis was established as clinical routine using the criteria established by the DSM-5. This diagnosis was registered at EHR, previously established by an experienced clinician, and confirmed by other psychiatric clinician to present study (b) living in residential facilities linked to Alicante Health Department - General Hospital, (c) diagnosed with an ID (intelligence quotient <70 scores) with problems in the regular development of communicative ability, and (d) participants and/or legal guardians who have received information about the design and purposes of the study, and gave their informed consent.

Procedure

The first step in our local pharmacovigilance system implementation consisted in a retrospective review, past 24 months of participants' EHRs. Two clinical pharmacologists specialized in neurodevelopmental and psychiatric conditions, evaluated participants' EHRs to identify AEs described as symptoms following these steps: (a) First, researchers examined locally hospital records using the National Integrated Health Information System, named in our region ABUCASIS; (b) Second, suspected adverse drug reactions (ADRs) registered in participants EHRs and reported to the National Pharmacovigilance Centre, if any, were reviewed and added to the study database; (c) Third, they had access to residential facilities internal electronic records of participants clinical events to complete study data base; and (d) Finally, after cautious review of all document sources, all ongoing medications during those 24 months were registered in study data base, including dosage and prescription duration. Drug prescription is usually updated in EHR by the nurse service and/or health providers that attend to autistic residential facilities. After that, as a quality control of the database records, all safety and medication data entered were also reviewed by a third clinical pharmacologist and a pharmacist from the study research team. All AEs or ADRs identified by researchers, were classified following the standard terminology established in "Medical Dictionary for Regulatory Activities" (MedDRA, see: http://www.meddra.org) as "Preferred terms" and "Classification by group and systems." Any ongoing medication potentially implicated in AEs or ADRs was classified through its chemical, pharmacological, and therapeutic properties according to standards defined by the Anatomical, Therapeutic, Chemical (ATC) classification of the World Health Organization (WHO, http://www.whocc.no). "Other" pharmacological group included drugs scarcely prescribed such as: pregabalin to target anxiety and challenging behaviors.

Pharmacovigilance monitoring system

As a second step, the research team adopted locally the following pharmacovigilance monitoring steps into the implemented system in a prospective manner for 12-months: (1) to attend to each of the four autism residential facilities and review their internal EHRs twice a month; (2) to update in the study database drug safety information reflected on local EHRs; and (3) finally, to analyze any potential new side effect, related with a new prescription or a dosage change, and not included as an AE in the EHR (Kelly et al., 2009).

Causality attribution of drug side effects

The retrospective part of the present study made us unable to impute certain AE to a participants' ongoing medication. Some information such as: temporal sequence, response pattern, withdrawal, re-exposure, alternative causes, placebo response, drug levels in tissues and body fluids, dose–response relationship, previous experience of the patient with the drug, or confirmation with objective tests, was lacking so causality attribution was impossible. When reviewing the symptoms described in participants' EHRs, researchers verified a potential side effect with drug information from the summary of product characteristics (SmPC) found in the Spanish Drug Regulatory Agency website. If researchers were unable to verify an AE to a suspected drug according to available data, it was labeled as "owing to unknown causes," and if certain side effect was caused by several medications, all were annotated individually.

AEs observed-to-expected (O/E) ratio

Furthermore, AE observed-to-expected (O/E) ratio was calculated according to SmPC information found in the Online Medicine Information Centre of the Spanish Drug Regulatory Agency (https://cima.aemps.es). This ratio was based on the frequency of the AEs "observed" in our population (e.g., identified when reviewing each participants' EHR), divided by what was "expected" by each drug according to SmPC safety data (Hastings et al., 2008). Ratio total score could be <1, corresponding to those cases where certain AE is observed less frequently than expectancy rates; score equals to 1 means that certain AE is found in the study with the same frequency as previously described in SmPC; >1 score in the study, represents an appearance more frequent than expected according to data available.

Statistical analysis

Quantitative variables of the project were presented as mean ± standard deviation or median and interquartile range (IQR). The qualitative variables were presented as percentages. An adaptation of the Cochran–Mantel–Haenszel test (Yu & Gastwirth, 2008) is used to show the O/E ratio values obtained, stratified by drug and using a color code to highlight the most extreme results. All data management and analyses were performed using Excel Version 19.0 (Microsoft, United States), GraphPad-Prism 5.0 software, and R Studio 3.6.1. for Windows.

RESULTS

Participants' EHR from ABUCASIS and the four different mental health residential facilities were reviewed between January 2015 and January 2018. For further details of sample inclusion see Figure 1, and please read the previous results (Espadas et al., 2020). Our sample consisted of 83 adults with ASD who were mainly male (86%), aged 20–40 years old. Epilepsy had the highest rate of psychiatric comorbidity, present in 33% of participants, other conditions were also prevalent such as insomnia (18%) or psychotic agitation (16%). Three hundred and sixty-five prescriptions were recorded, with a median (IQR) of 4 (3–6) medications per subject. A total of 58% of participants were under the polypharmacy range. The prescription distribution according to the pharmacological group was: 50% antipsychotics (47% with >1 antipsychotic simultaneously), 22% anticonvulsants, 16% anxiolytics, and 12% antidepressants, as shown in Figure 2.

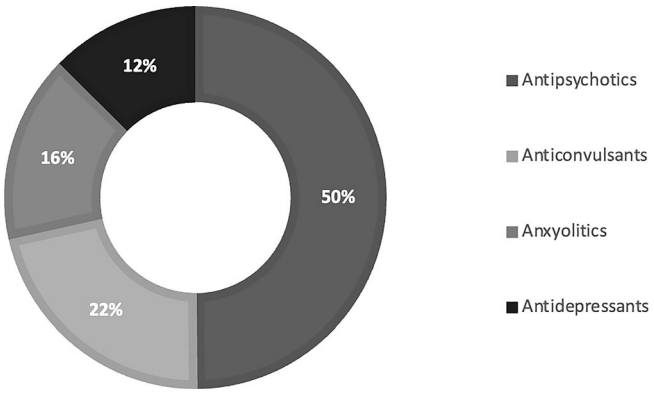

FIGURE 2 Prescription percentages of each pharmacological group for the 83 participants of the study

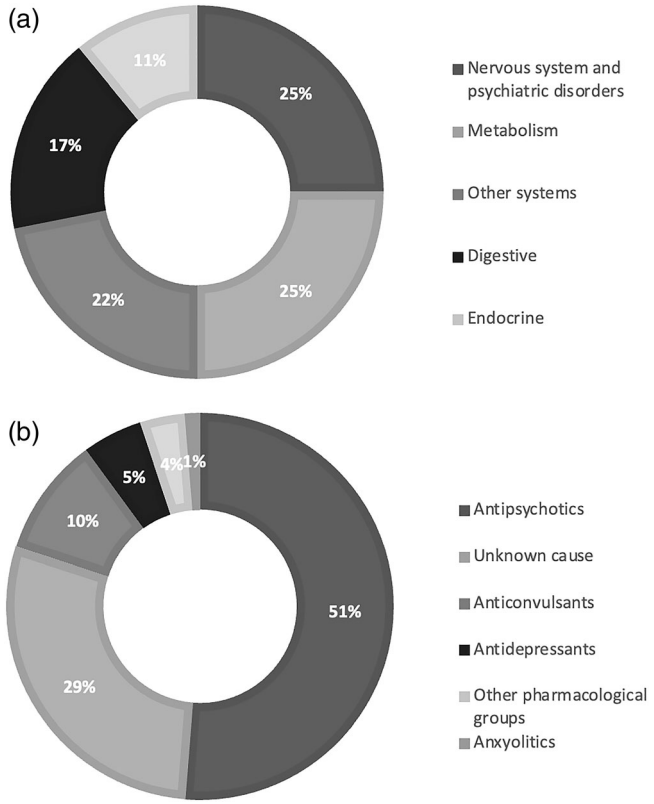

FIGURE 3 Main body systems affected by adverse events (AEs, $n = 64$) recorded (a) ongoing drugs potentially implicated in the suspected AEs (b) in autistic participants with intellectual disability (ID)

Drug and AEs potentially related

Figure 3 shows the main body systems affected by AEs identified, and ongoing medications classified by ATC, which were potentially implicated in AEs, according to information in SmPC and experts consideration. A total of 64 AEs were detected, half of them affected nervous and metabolic systems. The most prevalent AEs were hypercholesterolemia (17%), extrapyramidalism (12%), and constipation (11%). However, any symptom was notified to the National Pharmacovigilance System as ADR according to EHR information.

Up to 52% of total prescriptions (28 unique active ingredients) were related to identified AEs. Antipsychotics

TABLE 1 Body systems affected by adverse events (AEs) according to ongoing prescriptions information in summary of product characteristics (SmPC) in autistic participants with intellectual disability (ID)

System organ classification categories	Adverse events (AEs)	Ongoing drug prescriptions
Nervous diseases (16/64)	Asthenia (1/83)	Atomoxetine (1/1)
	Drowsiness (2/83)	Topiramate (1/2)
		Quetiapine (1/2)
	Extrapyramidalism (10/83)	Levomepromazine (1/10)
		Risperidone (1/10)
		Haloperidol (2/10)
		Periciazine (1/10)
		Paliperidone (1/10)
		Olanzapine (1/10)
		Levomepromazine + Haloperidol + Olanzapine (1/10)
		Paliperidone + Zuclopenthixol (1/10)
		Unknown cause (1/10)
	Headache (2/83)	Paliperidone + Sertraline (1/2)
		Risperidone (1/2)
	Neuroleptic syndrome (1/83)	Haloperidol (1/1)
Metabolism diseases (16/64)	Hypercholesterolemia (14/83)	Risperidone (1/14)
		Haloperidol (1/14)
		Olanzapine (1/14)
		Valproic acid + Clozapine (1/14)
		Unknown cause (10/14)
	Obesity (1/83)	Olanzapine + Valproic acid (1/1)
	Weight loss (1/83)	Tiapride (1/1)
Digestive diseases (11/64)	Constipation (9/83)	Risperidone (1/9)
		Risperidone + Clorazepate (1/9)
		Clonazepam + Levetiracetam (1/9)
		Unknown cause (6/9)
	Dysphagia (1/83)	Clozapine (1/1)
	Diarrhea (1/83)	Valproic acid (1/1)
Endocrine system (7/64)	Gynecomastia (2/83)	Androcur (1/2)
		Risperidone (1/2)
	Hyperprolactinemia (4/83)	Risperidone (1/4)
		Clomipramide (1/4)
		Risperidone + Amisulpride (1/4)
		Risperidone + Ziprasidone (1/4)
	Hypothyroidism (1/83)	Lithium (1/1)
Other adverse events (14/64)	Abdominal pain (1/83)	Topiramate (1/1)
	Acute urinary retention (1/83)	Biperiden + Zuclopenthixol + Olanzapine + Levomepromazine (1/1)
	Elevated transaminases (3/83)	Unknown cause (3/3)
	High blood pressure (1/83)	Unknown cause (1/1)
	Hypocalcaemia (1/83)	Unknown cause (1/1)
	Hypoglycaemia (1/83)	Pregabalin (1/1)
	Hyperuricemia (2/83)	Risperidone + Ziprasidone (1/2)
		Unknown cause (1/2)
	Low blood pressure (1/83)	Chlorpromazine + Fluvoxamine + Carbamazepine (1/1)
	Rhabdomyolysis (1/83)	Chlorpromazine + Fluvoxamine (1/1)
	Tachycardia (1/83)	Methylphenidate + Atomoxetine (1/1)
	Pulmonary thromboembolism (1/83)	Asenapine (1/1)

TABLE 2 Adverse event (AE) observed-to-expected (O/E) ratio according the summary of product characteristics (SmPC) found in the Spanish medicine and health products regulatory agency (CIMA, AEPMS, Spain), see methods section to better understand this calculation

	Risperidone	Olanzapine	Paliperidone	Valproic acid	Fluvoxamine	Clorazepate
Headache	**O/E: 0.12**		**O/E: 0.12**			
Diarrhoea				**O/E: 0.12**		**O/E: 6.62**
Constipation	**O/E: 1.32**					
Extrapyramidalism	**O/E: 6.62**	**O/E: 13.25**	**O/E: 13.25**			
Gynecomastia	**O/E: 6.62**					
Hypercholesterolemia	**O/E: 6.62**	**O/E: 0.66**		**O/E: 120.48**		
Hyperprolactinaemia	**O/E: 1.98**					
Hyperuricemia	**NO SmPC**					
Hypotension					**O/E: 6.62**	
Obesity		**O/E: 0.66**		**O/E: 120.48**		
Rhabdomyolysis					**NO SmPC**	
Urinary retention		**O/E: 6.62**				

displayed the highest number of identified AEs (51% of total AEs), followed by a 9% attributed to anticonvulsant prescriptions, and 5% to antidepressants. By contrast, anxiolytics were the least reported (1%). It should be highlighted that 29% of identified AEs were classified as "owing to unknown causes."

Table 1 gathers body systems affected by identified AEs related to participants ongoing medications according to information from SmPC. Antipsychotics were mainly associated with identified AEs affecting the nervous system (39%). Likewise, they were related with AEs in endocrine (17%), metabolic (15%), and cardiovascular (7%) systems. Risperidone caused one quarter of all AEs imputed to antipsychotics, and 13% of total AEs identified, either alone or combined with amisulpride or ziprasidone. They were mainly headaches, constipation, extrapyramidalism, gynecomastia, hypercholesterolemia, hyperprolactinemia, and hyperuricemia. To a lesser extent, olanzapine or paliperidone were also associated with many of the AEs found, as well as olanzapine with a case of urinary retention.

Anticonvulsants were mainly associated with metabolic and digestive systems AEs (29% respectively). Valproic acid was associated with most AEs (43%), mainly found in the digestive and metabolic systems (e.g., hypercholesterolemia, obesity, or diarrhea). From the antidepressant medications, only fluvoxamine, clomipramine, and sertraline were associated with identified AEs (e.g., headache, hyperprolactinemia, hypotension, or rhabdomyolysis). Finally, clorazepate, an anxiolytic, was related with the appearance of constipation, and "other" pharmacological group had various identified AEs related with their mechanism of action (e.g., gynecomastia after an antiandrogenic drug).

AEs observed-to-expected (O/E) ratio

AEs O/E ratios were calculated after retrospective and prospective revision of participants EHRs and safety information in SmPC, results are in Table 2.

Extrapyramidalism, gynecomastia, or hypercholesterolemia occurred more frequently than established values (O/E values >1). In this study, olanzapine caused the AEs of urinary retention and extrapyramidalism in a higher frequency than what was previously described in clinical studies. Similarly, extrapyramidalism linked to paliperidone presented a higher appearance rate than the prevalence described. Furthermore, hyperuricemia O/E Ratio due to risperidone and ziprasidone medications could not be calculated, as it was not described previously in SmPC data.

Regarding valproic acid, AEs described as "very rare side effects" according to SmPC data, were identified in the study, for example, hypercholesterolemia and obesity with 83 participants. Similarly, fluvoxamine and clorazepate were linked to infrequent AEs, such as obesity or rhabdomyolysis, and diarrhea, respectively.

DISCUSSION

After exploring the general safety of regular prescriptions in adults with ASD and ID, results confirm the challenge of detecting AEs in adults with ASD and ID without the presence of the local pharmacovigilance system, and even less to report ADRs to National Pharmacovigilance System. In this study, the AE identification was made by experts from our research team, as they were previously

reported in EHR as novel symptoms, but not connected to any medication taken. Given that half of our sample is under a chronic polypharmacy use, mostly antipsychotic drugs as risperidone, the total 64 AEs found in 3 years of analysis and 83 participants is low, as well as the zero ADRs reported in our Health Department. Furthermore, the activation of this local pharmacovigilance system was critical to identify serious and unexpected AEs. Physicians need training and support to be able to detect (AE) and report (ADR) issues related to medication safety during their practice. It is relevant, as nowadays, is the only way to increase information about pharmacological tolerability in naturalistic conditions.

First, our results showed a high polypharmacy rate amongst our participants, like that reported in previous studies in population with ASD (Lake et al., 2014; Spencer et al., 2013a). Our study suggests that adults with ASD may have possible off-label use of medication due to polypharmacy rate and the scarce information in EHR about participants' multiple comorbidities. The lack of pharmacological treatments for ASD core symptoms may also play a role in the off-label use of medication. According to data from Drug Regulatory Agencies, *Food and Drug Administration*, and *European Medicament Agency*, only risperidone and aripiprazole are approved for ASD-associated symptoms. However, any drug has proven efficacy for autism core symptoms. Even more, the polypharmacy prescription pattern has raised concerns worldwide, and some initiatives such as Stopping Overuse of Medication in People with Learning Disabilities and/or autism campaign have been developed (Park et al., 2016). This initiative tries to highlight inappropriate prescribing, perpetuation, and overuse of psychotropic medication in people with autism and/or ID. However, psychotropic medication deprescription is challenging due to limited alternative interventions, the requirement of a multidisciplinary team of experts, family support, and guidance from professionals, none of the above is usually included in healthcare regular practice (McNamara et al., 2017).

Surprisingly, despite polypharmacy rates, our AE average per subject was low (less than 1 AE/subject). So, further research is needed to differentiate which of present known comorbidities could be due to a chronic past AEs, consequence to long-term pharmacological treatment. A recent review in participants with ASD (Goel et al., 2018) described that side effects are displayed in up to 20% of participants in clinical trials using a single drug. Furthermore, in a large pharmacovigilance surveillance about psychotropic medications ($n = 613$), the overall incidence of ADRs was 1.6 (ranging from 1 to 8) per patient (Lucca et al., 2016). Incidence was higher in patients receiving 3–4 simultaneous drugs ($n = 220$), or if mental comorbidities were present ($n = 152$). An unidentified AE would lead to a prescription cascade associated to a symptom, and therefore its perpetuation. Several AEs could be preventable or avoidable, either with drug withdrawal or dose change and close monitoring, especially relevant in those patients who receive multiple medications simultaneously. To end up, an early detection and prevention of potential AEs may result in improved therapeutic outcomes and decreased unnecessary healthcare use. What's more, in our study some AEs were frequently identified (extrapyramidalism, gynecomastia, or even more, hypercholesterolemia, and rhabdomyolysis by valproic acid), but nearly a third of them were not previously described in respective SmPC. Related to that, it is important to mention that none of those identified AEs were previously reported as ADRs to National Pharmacovigilance System nor registered in participants' EHR by providers.

Previous data showed the risk of developing gynecomastia when using risperidone is four times higher (RR = 3.91, 95% CI = 2.01–7.62), turning into five in adolescents and young adults (RR = 5.44, 95% CI = 1.50–19.74) (Etminan et al., 2015). As seen in our sample, lipidic disorders may be linked to new generation of antipsychotics, as it has been described that their usage increases the frequency of appearance (Howes et al., 2018), even more, when if we combine quetiapine with valproic acid (Liang et al., 2011). Another identified AE in our study were urinary tract symptoms, other authors have described them when atypical antipsychotics are used for behavioral disturbances of dementia in old adults (Hall et al., 2012). Furthermore, digestive diseases identified (such as diarrhea) up to six times more frequently and due to clorazepate may have something to do with disorders in gut microbiota already related with ASD condition and mood disorders (Mangiola et al., 2016).

However, many AEs were attributable to a predictable known pharmacological effect, and already described in SmPC, so they might be avoidable (Howard et al., 2007). AE underestimation is common in general population (Giardina et al., 2018), despite their economic impact on the health system (Wu et al., 2012). In line with that, in the present work, there was a unanimous feeling amongst researchers that some comorbidities were systematically underestimated and considered normal within the study population. In this study, the registry of obesity was clearly underrated in participants' EHR, being wrongly attributed as an ASD comorbidity nor related with prescription (Jakobsen et al., 2016; Youngster et al., 2014). This is important, because if the weight gain is associated to an ongoing treatment, it may predispose to other health problems, such as insulin resistance (Sidhu et al., 2017) and/or other metabolic syndromes. Hyperprolactinemia, a common risperidone long-term side effect found in our sample is usually accompanied by sexual dysfunction (Roke et al., 2012), however, any sexual disorder was registered in participants' EHRs, probably a symptom susceptible to underestimation.

The good news is that most AEs are dose- and/or time dependent, therefore could be prevented with a local pharmacovigilance system and close monitoring

implementation. That is the case of cardiovascular AEs from selective serotonin-reuptake inhibitors, for example, QT-prolonging effect (Spigset, 1999; Yamazaki-Hashimoto et al., 2015). Surprisingly, half of the AEs identified in this work were not included on SmPCs, as hyperuricemia related with a high dose, and/or long-term treatment of risperidone (Vanwong et al., 2016).

We would like to highlight that the high prevalence of polypharmacy amongst adults with ASD should be constantly monitored. Local Health Service should promote systematically a safety monitoring of ongoing medications, and a careful evaluation of potential AEs. Providers should play an active role in supervising the effects of long-term ongoing medications. Even more in ASD, where the clinical and scientific evidence to guide drug treatments remains limited, leading to a high variability of drug combinations. Healthcare providers should be trained in detecting indiscernible AEs, reduce polypharmacy, and avoid the perpetuation of pharmacological treatments (Dhaliwal et al., 2019), especially in patients with ASD and ID.

Strengths

Although there are several randomized controlled trials evaluating psychotropic efficacy and safety (Ichikawa et al., 2017; Loebel et al., 2016; Pandina et al., 2007; Stigler et al., 2012), evidence in participants with autism or regarding drug combinations is still limited. To the best of our knowledge, this study is the first in our country to examine the extent of identified AEs related with several simultaneous medications, amongst adults with ASD and ID with a naturalistic environment, and estimate the incremental rate of AEs, and O/E ratio for specific drugs. Finally, our work suggests that adults with ASD and ID may have possible off-label use of prescription drugs without any clinical routinely safety monitoring, this potential situation is supported by the lack of pharmacological treatments available for ASD core symptoms. The local implementation of the system during clinical visits could improve patients' health status and reduce healthcare systems costs (Vohra et al., 2016).

Limitations

Despite its various strengths, our study was limited in some ways. First, causality attribution to unique drugs was challenging, because identified AEs could be unexpected or independent from the known pharmacological action, so we emphasize the importance of individualizing treatment in patients with ASD and keep a close monitoring (Garon et al., 2017; Moyer et al., 2019). Furthermore, the list of pharmacology classes coded may not have been exhaustive, and some drugs provided via an inpatient pharmacy, could not be reflected in our results. In addition, the duration of treatments were not considered for the purpose of this project, so special consideration should be given as some AEs can be time dependant. Also, adults with ASD, apart from psychotropic medication (antipsychotics, anticonvulsants, antidepressants, and anxiolytics), they use sedatives/hypnotics, betablockers, or statins, whose AEs were not monitored in the present study. Definitions of polypharmacy have varied substantially across studies, so that may condition different rates and difficult comparisons between studies. Comorbid diagnoses to ASD and ID listed in participants' EHR may not always as accurate or comprehensive as in cognitively able subjects without ASD. In addition, we did not register some relevant variables as intelligence quotient scores, possible genetic causes, non-pharmacological treatments, or rehabilitation programs. Acknowledging that they certainly could affect patient's response to treatments. Also, we acknowledge that the retrospective component of the present study, together with the lack of control group are part of the relevant limitations that had to be considered when interpreting the results. Finally, the results of the present study are generated from adults with ASD and ID, and we need further studies with bigger sample sizes to confirm these results, and make them generalizable for a similar population. Therefore, we cannot assume that our results are generalizable to the whole autism spectrum (Griffiths et al., 2019).

CONCLUSION

The use of several simultaneous psychotropic drugs amongst adults with ASD implies a higher risk for identified AEs appearance. Half of the participants in this study were under the effects of polypharmacy, and despite some identified AEs were previously reported, nearly half of them were not described in drugs' SmPC. In this study, none of them were notified as ADRs to the National Pharmacovigilance System, they were identified as AEs by the local pharmacovigilance system, but previously described as symptoms in participants' EHR. That has led to an under-recorded AEs on EHRs, as obesity. Clinicians need to be encouraged and trained to monitor the potential risks that single or combined ongoing medications may have in adults with ASD. The lack of long-term safety monitoring systems in this population should be addressed in the future by healthcare providers and researchers.

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CONFLICT OF INTEREST

The authors declare there was no conflict of interest.

ETHICS APPROVAL

The protocol was approved by the Ethics Committee of Alicante General Hospital and carried out following the Declaration of Helsinki requirements, as well as the current legislation in Spain.

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