The prevalence of potential drug–drug interactions in adults with intellectual disability

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Abstract

Background

There is a high use of medications in adults with intellectual disability (ID). One implication of taking multiple medications is the potential for drug–drug interactions (DDIs). How- ever, despite this being well highlighted in the main- stream literature, little is known about the incidence or associations of DDIs in the ID population.

Methods

This study describes the prevalence, patterns and associations of potential DDIs in a total administrative sample of adults with ID known to services in Jersey. Demographic, health-related and medication data were collected from 217 adults known to ID services. Data were collected using a face-to-face survey. The Anatomical Therapeutic Chemical classification system was used to categorise medications, and Stockley's Drug Interaction Checker was used to classify potential DDIs. Drug– drug pairings were considered to be of clinical significance if they were to be 'avoided, adjusted, monitored or required further information'.

Results

Potential DDIs of clinical significance were common. Exposure to potential DDIs of clinical significance was associated with being female, taking more than five medications (polypharmacy), living in residential care and having more health conditions. A simple regression was used to understand the effect of number of prescribed medications on potential DDIs of clinical significance. Every prescribed drug led to a 0.87 (95% confidence interval: 0.72–1.00) increase in having a potential DDI of clinical significance.

Conclusion

Adults with ID who live in residential care, are female, exposed to polypharmacy and have more health conditions may be more likely to have potential DDIs of clinical significance. Urgent consideration needs to be given to the potential of DDIs in this population given their exposure to high levels of medication.

Keywords

adverse reaction, drug–drug interaction, intellectual disability, medication, polypharmacy

Introduction

People with intellectual disability (ID) have greater physical and mental health needs than the general population (Hughes-McCormack *et al.* 2018, Kinnear *et al.* 2018, McMahon and Hatton 2020). Health inequalities for people with ID start early in life and widen with age, with the age of death being distinctly earlier than the general population (Glover *et al.* 2017, Landes *et al.* 2020, O'Leary *et al.* 2018, Trollor *et al.* 2017). A direct consequence of poor health is the need for individuals with ID to take more medications to combat the influence of morbidity (Emerson *et al.* 2016, Arnold 1993, Hove *et al.* 2019, McMahon *et al.* 2020, O'Dwyer *et al.* 2019, O'Dwyer *et al.* 2016). There is a growing evidence base that describes the incidence and associations of polypharmacy and psychotropic polypharmacy in this population (Bowring *et al.* 2017, Haider *et al.* 2014, Lunsky and Modi 2017, O'Dwyer *et al.* 2018, O'Dwyer et al. 2016). A recent study (McMahon *et al.* 2020) has drawn attention to the need to consider the impact of adverse drug reactions in this population by considering the epidemiology of drug-drug interactions (DDI) given the potential to cause significant harm (Preston 2019).

A DDI can be defined as the effect that one drug has on another (Preston, 2019). They are considered pharmacokinetic when the absorption, distribution, metabolism or elimination of a drug is altered due to the presence of another drug (Palleria *et al.* 2013) or pharmacodynamic when interacting drugs have either additive or opposing effects (Preston 2019). Drug-drug interactions are an important consideration when prescribing medications for people with ID (McMahon *et al.* 2020).To date, the issue of DDIs has not been widely explored in people with ID, with most evidence found in the elderly population (Björkman *et al.* 2002, Juurlink *et al.* 2003, Novaes *et al.* 2017, Rodrigues and Oliveira 2016). Apart from Joos et al. (2016), Floch et al. (2018), and more recently, The Learning Disability Mortality Review (LeDeR) [2020], the present authors are not aware of other research investigating the presence of potential DDIs in the ID population. Both Joos et al. (2016) and Floch et al. (2018) identified a high proportion of potential DDIs in their studies. Joos et al (2016) cited Topiramate and Valproic acid as the most frequently occurring drug-pairing that

resulted in DDIs, while LeDeR (2020) highlighted a significant proportion of potential DDIs with Valproate products, Lamotrigine, Topiramate and Phenytoin being the most common.

Caution must be observed when interpreting evidence of potential DDIs, as they depend on many pharmacokinetic and pharmacodynamic factors. The risk of DDIs (Palleria *et al.* 2013; Kohler *et al.* 2000) and adverse drug reactions (Gnjidic *et al.* 2012) increases with the number of medications prescribed (Preston 2019). This presents a significant risk for people with ID, as they are more likely to have multiple health conditions, increased medication use, and communication difficulties, with some adults being unable to feedback side effects experienced (Kinnear *et al.* 2018, Smith *et al.* 2020).

This study builds upon the findings of previous research (McMahon *et al.* 2020) and describes the prevalence, patterns and associations of potential DDIs in a total administrative sample of adults with intellectual disability known to services in Jersey.

Method

Procedure

This study was undertaken in Jersey, Channel Islands, in a total administrative population sample of adults known to ID services. Further methodological details are available in the following (McMahon *et al.* 2020, McMahon and Hatton 2020, McMahon, Bowring and Hatton, 2019 and Bowring *et al.* 2017).

Setting and Participants

Jersey is a self-governing British Crown dependency with a population of just over 105 000 people (Government of Jersey, 2020). Of these inhabitants, approximately 86,000 are aged over 18. A previous meta-analysis indicating an administrative adult

ID prevalence rate of 4.94/1000 (95% CI: 3.66–6.22) (Maulik *et al.* 2011) would suggest that approximately 427 adults with ID may live in Jersey.

In sum, 285 adults with ID were known to services, and data were collected on 217, a 76% response rate [approximately 66.7% of all expected adults with ID in Jersey]. All individuals with ID in Jersey have access to specialist ID services that operate peripatetically. People with complex, physical, behavioural or psychiatric needs are assigned a community nurse who coordinates the necessary specialist health and social care support. All data were collected by a face-to-face survey and medication data were collected directly from prescription charts, individual medication administration records or by examining any medication the person had in their possession. Participants' degree of intellectual disability was administratively defined by Jersey's Health and Community Services in the participant's health and social care records. This classification was used to stratify the sample for analysis. Overall, 56.6% of the sample was male (n=122), the mean age of participants was 44.5 years (SD = 16.2, range = 18–84 years). Just under half of the sample had a mild ID (n=108), the mean number of ICD-10 conditions was 3.82 (SD=2.71), 24% of the sample had an epilepsy diagnosis (n=52), and over 50% (n=114) of participants had mental health or behavioural issues. Selected personal and health characteristics of participants are presented in Table 1.

Table 1 Demographic and health characteristics of the study population (n=217)

Characteristic	**N (%)**
Gender / Age	
Male	122 (56.2)
Female	95 (43.8)
Mean age in years	44.51 (SD: 16.24)
Degree of intellectual disability	
Mild intellectual disability	108 (49.8)
Moderate intellectual disability	56 (25.8)
Severe intellectual disability	34 (15.7)
Profound intellectual disability	19 (8.8)
Communication	
Never speaks a word	23 (10.6)
Uses a few words only	37 (17.1)
Speaks using sentences as normal	151 (69.6)
Can talk but does not speak	6 (2.8)

Polypharmacy	
No Polypharmacy	134 (61.8)
Polypharmacy (≥5 medications)	83 (38.2)
Psychotropic Polypharmacy	
No Psychotropic Polypharmacy	167 (77)
Psychotropic Polypharmacy (≥2 psychotropic medications)	50 (23)
Residence	
Non-residential care	110 (50.7)
Residential care	107 (49.3)
Down Syndrome	
Down Syndrome	29 (13.4)
No Down Syndrome	188 (86.6)
Epilepsy*	
Epilepsy Diagnosis	52 (24.0)
Query Epilepsy Diagnosis	3 (1.3)
No Epilepsy Diagnoses	162 (74.7)
Psychiatric disorder diagnosed over the life course*	
Psychiatric disorder	73 (33.6)
Unable to ascertain if disorder diagnosed over the life course	5 (2.3)
No Psychiatric disorder	137 (63.1)
Most prevalent ICD-10 Conditions	
Mental health illnesses or behavioural problems	114 (52.5)
Diseases of the musculoskeletal system	76 (35)
Diseases of the digestive system	75 (34.6)
Endocrine, nutritional or metabolic conditions	67 (30.9)
Diseases of the skin	67 (30.9)
Diseases of the genitourinary system	65 (30)
Neurological conditions	65 (30)
	(Mean, SD)
Number of ICD-10 Conditions	3.82 (2.71)

* Notes: Three participants did not have a definite diagnosis of epilepsy were excluded from analysis. It could not be determined in five instances if participants had a psychiatric disorder diagnosed over the life course and these were also excluded from analysis.

Ethical Approval

Ethical approval was granted from the Faculty of Health and Medicine Research Ethics Committee at Lancaster University and by the Government of Jersey, Health and Community Services Ethics Committee. Procedures for recruiting participants lacking capacity and including arrangements for identifying and consulting consultees were developed using guidance from the Mental Capacity Act (2005) and the Health Research Authority (www.hra.nhs.uk).

Measures

Demographic and health data on each participant, for example, gender, age, residence, communication ability and health conditions using ICD-10 classification Chapter headings (McMahon and Hatton, 2020), was collected from face-to-face surveys with the participant or proxy informant. Medication data were collected on the medications the participant was prescribed, dosage, and whether the medication was prescribed regularly, for a short course basis, or on a 'pro re nata' (PRN) basis. PRN medication was included if it had been prescribed in the previous 28-day prescribing cycle by a medical prescriber. Our study included inhalation and transdermal routes of delivery but excluded topical agents that were applied as gels, creams, or ointments; as primary topical delivery systems are designed to deliver the active ingredient to local tissue so the risk of the drug entering systemic circulation is negligible (Benson *et al.* 2019). All data were cross-checked with the individual's electronic health and social care record and any inconsistencies were resolved with the community nurse.

All medications that participants took during the previous 28 days cycle were coded according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) [WHO, 2020] classification system and then entered into Stockley's Interactions Checker on the Medicines Complete platform (https://about.medicinescomplete.com). This interaction checker gives a description of the interaction under '*severity'* level; provides guidance on the management of the interaction under '*action',* and describes the weight of research behind the interaction under 'evidence'. Brief guidance of this is outlined in Appendix 1 to assist interpretation. To generate a dependent variable, we operationalised that potential DDIs were clinically significant if drug-drug interacting pairs were to be *'avoided, adjusted, monitored or required further information'*.

Approach to analysis

The study took the following analytical approach. Firstly, we undertook descriptive statistics (mean, standard deviation, sum, range) to describe the frequency and cumulative incidence of demographic variables, medication use and potential DDIs. Secondly, inferential statistics were used (Mann-Whitney U test and Kruskal-Wallis H test) to test the null hypothesis that there was no statistical difference between independent groups and potential clinically significant DDIs (dependent variable). In the final stage of analysis, we used linear regression to assess the relationship between the number of prescribed drugs (independent variable) and potentially clinically significant DDIs. Statistical significance was accepted at the ≤0.05 level of probability in all analysis.

Results

In terms of medication, 83.4% (n = 181) of participants were prescribed at least one medication (mean = 4.58, SD = 4.42, range = 1–21) while 38.2% of participants were exposed to polypharmacy (≥5 medications) (O'Dwyer et al. 2016). The most frequently prescribed category of drugs from the ATC classification system were: neurologicals (n=375); alimentary tract and metabolism (n=255); dermatologicals (n=133); cardiovascular drugs (n=87) and drugs for the respiratory system (n=81). The five most frequently prescribed drugs were Paracetamol (n=58), Valproate (products) (n=34), Simvastatin (n=22) Risperidone (n=21) and Procyclidine (n=21).

In total, 519 potential DDIs of clinical significance were identified. 199 of these pairings needed to be avoided, adjusted or required close monitoring and 320 of these pairings required further information regarding potential interactions and adverse effects. Across all drug-drug pairings, in 235 instances, no DDIs of any potential clinical significance were identified. 105 participants had at least one potential DDI of clinical significance (mean=4.94 SD=4.84, range 1-25). Twenty-four drug combinations were recorded as needing adjustment. This primarily concerned the concomitant use of Lorazepam and Valproate products (study evidence) [n=7],

Levothyroxine and Calcium supplements (case evidence) [n=6]; the remainder broadly concerned pharmacokinetic drug interaction mechanisms that alter disposition (absorption, distribution, elimination) of a co-administered agent.

In the next stage of analysis, we identified combinations of drugs that had potentially severe outcomes when co-administered with another drug. Citalopram (n=13), Risperidone (n=21) and Valproate (products) (n=34) were the three most frequently prescribed drugs that had potentially severe outcomes when co-administered with another drug. Table 2 provides an overview of the frequencies of these potential DDIs and an overview of how these drugs potentially interacted with a range of other drugs where the source of evidence came from published studies only. These combinations, along with a brief overview of interactions are outlined.

Table 2: Potential drug-drug Interaction combinations of the top three drugs (Citalopram, Risperidone and Valproate) causing severe outcomes

ATC Interacting drug combination(s)	Drug names	Action	Brief overview of potential drug-drug interaction from UpToDate (Lexicomp)(February 2021)
Frequency: 13 participants were prescribed Citalopram and this was responsible for 24 potential DDIs in the study. The following are potential DDIs that are associated with severe outcomes and underpinned by study evidence.			
N06AB04+N06AA09	Citalopram & Amitriptyline (n=1)	Information	▪ Amitriptyline may enhance the serotonergic effect of Citalopram and also increase the serum concentration of Citalopram. Citalopram may increase the serum concentration of Amitriptyline.
N06AB04+N05AH02 OR N05AH04	Citalopram & Clozapine (n=1)/ Quetiapine (n=1)	Information/ monitor	▪ Citalopram may enhance the adverse/toxic effect of certain antipsychotic drugs. QT- Antipsychotics may enhance the QTc-prolonging effect of QT-prolonging Antidepressants.
N06AB04+M01AC06 OR M01AE02	Citalopram & Meloxicam (n=1) / Naproxen (n=2)	Information	▪ Citalopram may enhance the antiplatelet effect of Nonsteroidal Anti-Inflammatory Agents (Nonselective). Nonsteroidal Anti-Inflammatory Agents (Nonselective) may diminish the therapeutic effect of Citalopram.
N06AB04+A02BC01 OR A02BC03	Citalopram & Omeprazole (n=1) / Lansoprazole (n=1)	Monitor/ information	▪ Omeprazole and/or Lansoprazole may increase the serum concentration of Citalopram.
Frequency: 21 participants were prescribed Risperidone and this was responsible for 34 potential DDIs in the study. The following are potential DDIs that are associated with severe outcomes and underpinned by study evidence.			
N05AX08+N06AA09	Risperidone & Amitriptyline (n=1)	information	▪ Anticholinergic Agents may enhance the adverse/toxic effect of other Anticholinergic Agents. CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants. Serotonergic Agents may enhance the adverse/toxic effect of Antipsychotic Agents. Specifically, serotonergic agents may enhance dopamine blockade, possibly increasing the risk for neuroleptic malignant syndrome. Antipsychotic Agents may enhance the serotonergic effect of Serotonergic Agents. This could result in serotonin syndrome.
N05AX08+N06AB03	Risperidone & Fluoxetine (n=1)	Monitor	▪ CYP2D6 Inhibitors may increase the serum concentration of Risperidone.
N05AX08+C03CA01	Risperidone & Furosemide (n=2)	Information	▪ Loop Diuretics may enhance the adverse/toxic effect of Risperidone
N05AX08+N06AX16	Risperidone & Venlafaxine (n=1)	Information	▪ Serotonergic Agents may enhance the adverse/toxic effect of Antipsychotic Agents. Specifically, serotonergic agents may enhance dopamine blockade, possibly increasing the risk for neuroleptic malignant syndrome. Antipsychotic Agents may enhance the serotonergic effect of Serotonergic Agents. This could result in serotonin syndrome.

34 participants were prescribed Valproate products and this was responsible for 31 potential DDIs in the study. The following are potential DDIs that are associated with severe outcomes and underpinned by study evidence.

N03AG01+N03AF01	Valproate & Carbamazepine (n=7)	Monitor	▪ Valproate products may increase serum concentrations of the active metabolite(s) of Carbamazepine. Parent carbamazepine concentrations may be increased, decreased, or unchanged. Carbamazepine may decrease the serum concentration of Valproate products.
N03AG01+ N03AB02	Valproate & Phenytoin (n=1)	Monitor	▪ Valproate products may decrease the protein binding of Fosphenytoin-Phenytoin.
N03AG01+N03AX11	Valproate & Topirimate (n=2)	Monitor	▪ Topiramate may enhance the adverse/toxic effect of Valproate Products.
N03AG01+N03AX09	Valproate & Lamotrigine (n=1)	Monitor	▪ Valproate products may enhance the adverse/toxic effect of Lamotrigine. Valproate products may increase the serum concentration of Lamotrigine.
N03AG01+N03AA03	Valproate & Primidone (n=1)	Monitor	▪ Valproate products may decrease the metabolism of Primidone. More specifically, the metabolism of phenobarbital, primidone's primary active metabolite, may be decreased. Primidone may increase the serum concentration of Valproate products.

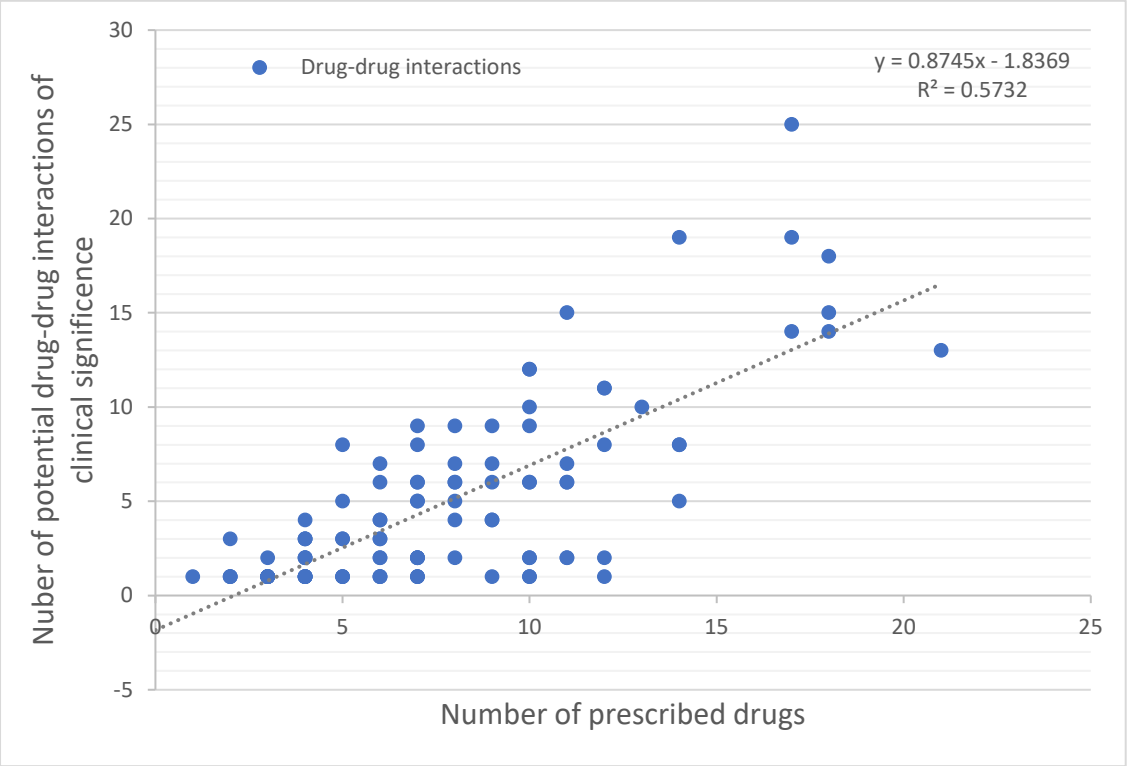
In the second stage of analysis, it was determined that being female (U = 1054.5, p = .047), polypharmacy (U=339.0, p<.001), living in residential care (U=983.0, p=0.033) and having more health conditions (as measured by ICD-10 classification) (H (17) = 31.71, P = .016) was associated with exposure to potential DDIs of clinical significance. There was no statistical association between exposure to potential DDIs of clinical significance and age ((H (17) = 21,48, P = .206), severity of ID (U =1227.0, p=.498), having had a psychiatric disorder diagnosed over the life course (U =1165.5, p=.364), Down syndrome (U=343.0, p=.143) or epilepsy (U=1113.0, p=.396). Potential DDIs of clinical significance were statistically more likely people who had endocrine, nutritional and metabolic disease (p <0.001), diseases of the ear (p=0.029), respiratory system (p <0.001), circulatory system (p <0.001), musculoskeletal system (p=0.021), genitourinary system (p=0.044), malformations and genetic problems (p=0.021) and injuries as a result of trauma and poisoning (p=0.041).

The incidence of required action by the severity of ID was also examined. There was no statistical difference observed across the degree of ID and adjusting (H (3) = 3.62, P = .305), monitoring (H (3) = 6.39, P = .094) or providing further information (H (3) = 1.10, P = .780) for potential clinically significant DDIs. We also examined the severity of potential DDIs and the ability to speak as the ability to self-report may be important for quickly identifying adverse effects. No statistically significant associations were observed (p = 0.54) identifying that there was no difference in the severity of potential DDIs across verbal and non-verbal participants.

In the final stage of analysis, a linear regression was undertaken to understand how the impact of prescribing drugs predicted the increase of potential DDIs of clinical significance (See Figure 1 for scatter diagram with linear regression line). The prediction equation was: number of potential drug-drug interactions of clinical significance = -1.792 + 0.870*number of prescribed drugs. Increased numbers of prescribed medications statistically predicted potential DDIs of clinical significance $F(1, 103) = 137.34$, $p < .0001$, accounting for 57.2% of the variation in potential DDIs of clinical significance $R^2 = 56.7\%$ (a medium size effect [Cohen 1988]). Every

extra prescribed drug increased the incidence of potential DDIs of clinical significance by 0.87 (95% CI: 0.72-1.00).

Figure 1: Scatterplot of potential drug-drug interaction vs. the number of prescribed drugs



Discussion

This study has identified a high prevalence of potential DDIs of clinical significance in an administrative population-level sample of adults with ID. Essentially, the more medications people with ID take, the greater the risk that an adverse reaction will occur (Preston 2015). This is important as people with ID are prescribed medications in high numbers and high doses. These findings are consistent with the current underdeveloped evidence base concerning pharmacological treatment in adults with ID (Floch *et al.* 2018; LeDeR 2020; Joos *et al.* 2016). These findings have important implications for a number of reasons: (1) the potential of developing DDIs of clinical significance is a genuine concern for this population. Just under half of this total administrative sample had at least one potential DDI of clinical significance and our study has illustrated that their incidence increases with the number of medications

prescribed. This concern is particularly acute in this population as they already expierence high levels of morbidity (McMahon and Hatton 2020) are frequently exposed to off label prescribing (for example, being prescribed psychotropic medications to manage challenging behaviour) [Bowring *et al.* 2017; Henderson *et al.* 2020] and such culumative effects may therefore negatively impact the health and wellbeing of this population. (2) Our results are similar to both Joos et al. (2016) and LeDeR (2020) who both identified that antiepileptics and Valproate products, in particular, are most commonly involved in potential DDIs. This study has identified that Valproate and Carbamazepine was the most frequently prescribed drug pairing that may produce severe DDIs. This underpins the need to ensure that there are comprehensive therapeutic drug monitoring regimes for individuals who are prescribed antiepileptic monotherapy or polytherapy to monitor for drug concentration levels. While this study had lower frequencies of antiepileptic combinations than Joos et al. (2016), their study was undertaken in an institution where participants were administered medications through enteral feeding tubes and nearly 50% were prescribed Valproate. (3) This study also identified specific cases where the concomitant use of medications such as Valproate and Lorazepam is a source for concern and prescribing adjustment may be necessary. For example, Valproate may increase the serum concentration of Lorazepam and decrease Lorazepam clearance, which could lead to augmented sedation (Samara *et al.* 1997). As Lorazepam is often prescribed as a PRN medication for people who have behaviours that challenge (Deb *et al.* 2015) the full effects of such an interaction may only manifest when an individual is in an already distressed state. (4) Being female, living in residential care, taking more than five medications (polypharmacy) and having greater health needs were associated with exposure to potential DDIs of clinical significance. It is important to highlight that having had a psychiatric disorder diagnosed over the life course, or epilepsy, was not associated with having statistically significantly higher numbers of potential DDIs of clinical significance, but the drugs used to treat such conditions are commonly associated with greater severity of potential DDIs. One reason for this may be that as every extra prescribed drug led to a 0.87 increase of having a potential DDI of clinical significance, then greater levels of poor health (for example, having more ICD-10 conditions) is related to being prescribed more medications and consequent exposure to potential DDIs of

clinical significance. Subsequently, it is vitally important to ensure that there are regular health and medication reviews (Scheifes *et al.* 2016; Henderson *et al* 2020) for all people with ID along with appropriate training for staff to recognise DDIs and mitigate for diagnostic overshadowing (Mason and Scior 2004). (5) Given that our findings highlight that there were 320 instances where people should be provided with further information regarding potential adverse effects, there is also a critical need to ensure that people with ID are provided with an appropriate and understandable level of medication-related information (O'Dwyer *et al.* 2015). The Prescribing Competency Framework (RPS, 2016) in the UK sets out that prescribers have to understandably communicate potential unwanted effects; consequently, this should include potential DDIs to enable individuals to make informed decisions about treatment. This would assist people with ID to report any unwanted side effects. Additional adjustments should be made for individuals who have communication impairments. 6) Antiepileptics and psychotropic drugs are frequently involved in potential DDIs. As they are prescribed in high levels in this population (McMahon *et al.* 2020; Bowring *et al.* 2017; O' Dwyer *et al.* 2017) it is important that initiatives to stop inappropriate prescribing (e.g. stopping over medication of people [NHS, 2017]) are implemented and regularly evaluated to measure effectiveness as a matter of priority.

Notwithstanding these findings, there are important limitations of this study that need to be kept in mind. Frist, drug-drug interaction programs are known to report clinically minor or theoretical interactions, and this is likely to overestimate the prevalence of potentially relevant clinical DDIs (Kheshti *et al.* 2016, Muhič *et al.* 2017). Second, the sample was small and the self-reporting and proxy nature of the study increases the potential of information bias. Third, the inclusion of PRN medication prescribed within the previous 28 days may inflate the prevalence of medication use. Fourth, side effects potentially caused by DDIs were not assessed during data collection. This should be considered in future studies. Fifth, the presence of "requires further information" in the definition of potentially clinically significant DDIs may be considered overly inclusive. However, it was determined that even potential DDIs that 'require further information' can have a severe impact which could incapacitate or result in either a permanent detrimental effect or a life-

threatening event. Consequently, their inclusion was considered necessary and proportionate to the identified risks.

Implications for Practice

While it is not possible to determine if medications were clinically justified and "appropriately" or "inappropriately" prescribed in this study, this brief report does offer some insight into the frequency and severity of potential DDIs that this population may experience. As far as we are aware, such data has not been published at a population level. The clinical implications of this study underline that frequent health and medication reviews are critically important (Scheifes *et al.* 2016). This is especially the case where individuals are prescribed antiepileptic and psychotropic drugs as these were associated with the greatest severity of potential DDIs. As there is still limited data supporting the efficacy and safety of most commonly employed psychotropic drug combinations in this population (O'Dwyer *et al.* 2017) such prescribing warrants careful contemplation. Nonetheless, as with all prescribing decisions, clinicians need to consider the risks and benefits and weigh up the intended outcome vs quality of life in consultation with the patient and relevant others.

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Appendix 1: Stockley's drug interaction guidance

- **Action**: This describes whether or not any action needs to be taken to accommodate the interaction. This category includes 'avoid', 'adjust', 'monitor', 'provide further information' and 'no action needed'.
- **Severity**: This describes the likely effect of an unmanaged interaction on the patient. This category includes 'nothing expected', 'mild', 'moderate', 'severe', and 'unknown'.
- **Evidence**: This describes the weight of evidence behind the interaction. This category includes 'theoretical', 'case', 'study' and 'extensive'.