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# Identification of different side effects between PARP inhibitors and their polypharmacological multi-target rationale

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**Aims:** The aim of this study was to determine the differences and potential mechanistic rationale for observed adverse drug reactions (ADRs) between four approved PARP inhibitors (PARPi).

**Methods:** The Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card drug analysis profiles and NHS secondary care medicines database enabled the identification of suspected ADRs associated with the PARPi in the UK from launch to 2020. The polypharmacology of the PARPi were data-mined from several public data sources.

**Results:** The overall ADRs per 100 000  $R_x$  identified across the four PARPi are statistically significant ( $\chi^2$  test,  $P < .001$ ). Rucaparib has the greatest relative suspected ADRs, which can be explained by its least clean kinome and physicochemical properties. The suspected gastrointestinal ADRs of rucaparib and niraparib can be ascribed to their kinase polypharmacology. Suspected blood and lymphatic system ADRs of PARPi can be linked to their high volume of distribution ( $V_d$ ). The thrombocytopenia rate of niraparib > rucaparib > olaparib tracked with the  $V_d$  trend.

Hypertension is only associated with niraparib and could be explained by the therapeutically achievable inhibition of DYRK1A and/or transporters. Arrhythmia cases are potentially linked to the structural features of *h*ERG ion-channel inhibition found in rucaparib and niraparib. Enhanced psychiatric/nervous disorders associated with niraparib can be interpreted from the diverse neurotransmitter off-targets reported.

**Conclusions:** Despite their similar mode of action, the differential polypharmacology of PARP inhibitors influences their ADR profile.

## KEYWORDS

clinical pharmacology, oncology, therapeutics

## 1 | INTRODUCTION

Poly-ADP ribose polymerase 1 (PARP1) inhibitors (PARPi) are a new class of agents for the treatment of solid tumours that

provided the first clinical exemplification of synthetic lethality in oncology.<sup>1</sup> The combination of a breast cancer type 1 susceptibility protein 1 or 2 (BRCA1 or BRCA2) mutation and PARPi leads to the inability of cancer cells to repair themselves.<sup>2</sup> PARPi show efficacy for high-grade and platinum-resistant cancers. Clinical trials have demonstrated that PARPi

The authors confirm that the principal investigator for this paper is Dr Alan M. Jones.

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increase overall survival time and response rate of cancer patients.<sup>3</sup>

The four PARPi included in this study are: **olaparib**, **niraparib**, **rucaparib** and **talazoparib**. The PARPi were first licensed in the UK in 2014 (olaparib),<sup>4</sup> 2017 (niraparib),<sup>5</sup> 2018 (rucaparib)<sup>6</sup> and 2019 (talazoparib),<sup>7</sup> respectively. Olaparib, niraparib and rucaparib are currently used in the clinic for the treatment of ovarian cancer,<sup>8–11</sup> fallopian cancer and peritoneal cancer,<sup>4–6</sup> whereas talazoparib is used in the clinic for the treatment of breast cancer.<sup>7</sup> Olaparib is also approved for prostate cancer. Indications in other cancer types are being investigated or pending regulatory approval.

PARPi trap PARP1/2 at DNA lesions, abolishing PARylation-mediated processes including DNA damage repair.<sup>12</sup> PARP–DNA complexes interfere with DNA replication, and PARP-trapping leads to PARPi cytotoxicity which explains the differential cytotoxicity of PARPi. Talazoparib is the most potent PARP-trapper identified.<sup>12</sup>

Adverse drug reactions (ADRs) are unwanted reactions which occur following drug administration. Approximately 6–7% of hospital admissions are due to ADRs, so the health and financial implications are significant.<sup>13</sup> ADRs are an important consideration with new medicines which have limited information about their safety in the wider population. The MHRA Yellow Card reporting scheme in the UK collects and monitors suspected medicine safety.

The occurrence of ADRs is not necessarily predictable based on a drug's specific therapeutic effect. Although the PARPi in this study have the same mechanism of action, their binding affinities to PARP isoforms and their polypharmacology are different. Studies have assessed the kinase polypharmacology of PARPi<sup>14</sup> or compared safety profiles<sup>15–21</sup> but have not investigated the relationship between polypharmacology and ADRs. Our continuing research interest in the intersection of medicinal chemistry<sup>22</sup> with clinical prescribing and associated ADRs<sup>23</sup> offered an opportunity to apply our techniques to better understand the PARPi drug class polypharmacology and its relationship to suspected ADRs.

## 2 | METHODS

### 2.1 | Prescribing data

NHS secondary care medicines data<sup>24</sup> was extracted on processed pharmacy stock from January 2019 to July 2020 (Figure S1 in the Supporting Information). Data before January 2019 are not publicly available due to publishing agreements with NHS trusts.

A formula was developed to estimate the total number of prescriptions dispensed from the processed pharmacy stock for each drug from January 2019 to July 2020:

$$\text{Prescriptions per month} = \frac{\text{Processed pharmacy stock} \times \text{Strength of drug}}{\text{Dose of drug} \times \text{Number of days in month}}$$

### What is already known about this subject

- Poly-ADP ribose polymerase 1 inhibitors (PARPi) have provided the first clinical exemplification of synthetic lethality in oncology.
- A diverse range of ADRs have been reported despite their similar mode of action.
- An explanation for this divergence in ADRs is needed.

### What this study adds

- Comprehensive data mining of the polypharmacology of PARPi in conjunction with the MHRA Yellow Card database identified emerging and predicted ADR signals.
- Despite their similar mode of action, the differential polypharmacology of PARPi influences their ADR profile.

Therefore, the suspected ADR rate of each PARPi (since their respective launch dates) is based on the prescribing data for the period January 2019–July 2020.

### 2.2 | Adverse drug reactions

Reported ADR data was extracted from the Yellow Card Interactive Drug Analysis Profile.<sup>25</sup> Data was available from the year each drug was licensed until August 2020. Significant ADRs were selected and assessed within this study. The selection criteria included differential ADRs across the PARPi (independent of ADR level above baseline) or high levels of ADR within a particular organ class (above baseline).

The ADR data required standardisation to allow for comparisons between the different drugs. ADRs per 100 000  $R_x$  is a standard approach in signal hypothesis generation.<sup>26</sup> A formula was developed to calculate the ADRs per 100 000  $R_x$ :

$$1) \text{ Scale factor} = \frac{100,000}{\text{Total number of prescriptions}}$$

$$2) \text{ ADRs per } 100\,000\,R_x = \text{ADR} \times \text{Scale factor}$$

Figures S2 and S3 in the Supporting Information represent the standardised data and reports of suspected fatal ADRs, respectively.

### 2.3 | Chemical properties and pharmacology

The Electronic Medicines Compendium<sup>27</sup> and ChEMBL database<sup>28</sup> were used to identify the chemical properties, pharmacokinetics and

pharmacology of the four PARPi (accessed on 20 October 2020 (Table 1). Parameters were calculated;  $pIC_{50}$  was calculated using the median PARP1  $IC_{50}$  of each drug; and lipophilic ligand efficiency (LLE) was calculated as  $LLE = pIC_{50} - clog_{10}P$ . An LLE value of  $<5$ , is associated with increased toxicity.<sup>29</sup> The threshold for BBB penetration was set as molecular weight  $<450$  Da;  $<6$  hydrogen bond donors (HBD);  $<2$  hydrogen bond acceptors (HBA); neutral or basic drug molecule (defined by  $pK_a$ ); topological polar surface area (tPSA)  $<90$  Å;  $\log D_{7.4}$  1–3 and low affinity to efflux ABCB1 (P-glycoprotein, MDR1).<sup>26</sup> The  $C_{max}$  peak serum concentration of each PARPi was calculated from FDA data.<sup>30–34</sup>

## 2.4 | Target affinity

The canSAR database (accessed on 5 November 2020)<sup>35–37</sup> was used to gather quantitative measures between each PARPi and human proteins. Bioactivity was compared using  $IC_{50}$  values, with a minimum threshold set at  $10 \mu M$  (to exclude weak interactions). Additional

information was extracted from niraparib's new drug application (NDA)<sup>38</sup> and literature.<sup>39</sup> The mean  $IC_{50}$  gives an overview of the relative affinity between PARPi across multiple targets (Figure 1) and mitigates for the reproducibility/reliability issue of selecting a single  $IC_{50}$ .

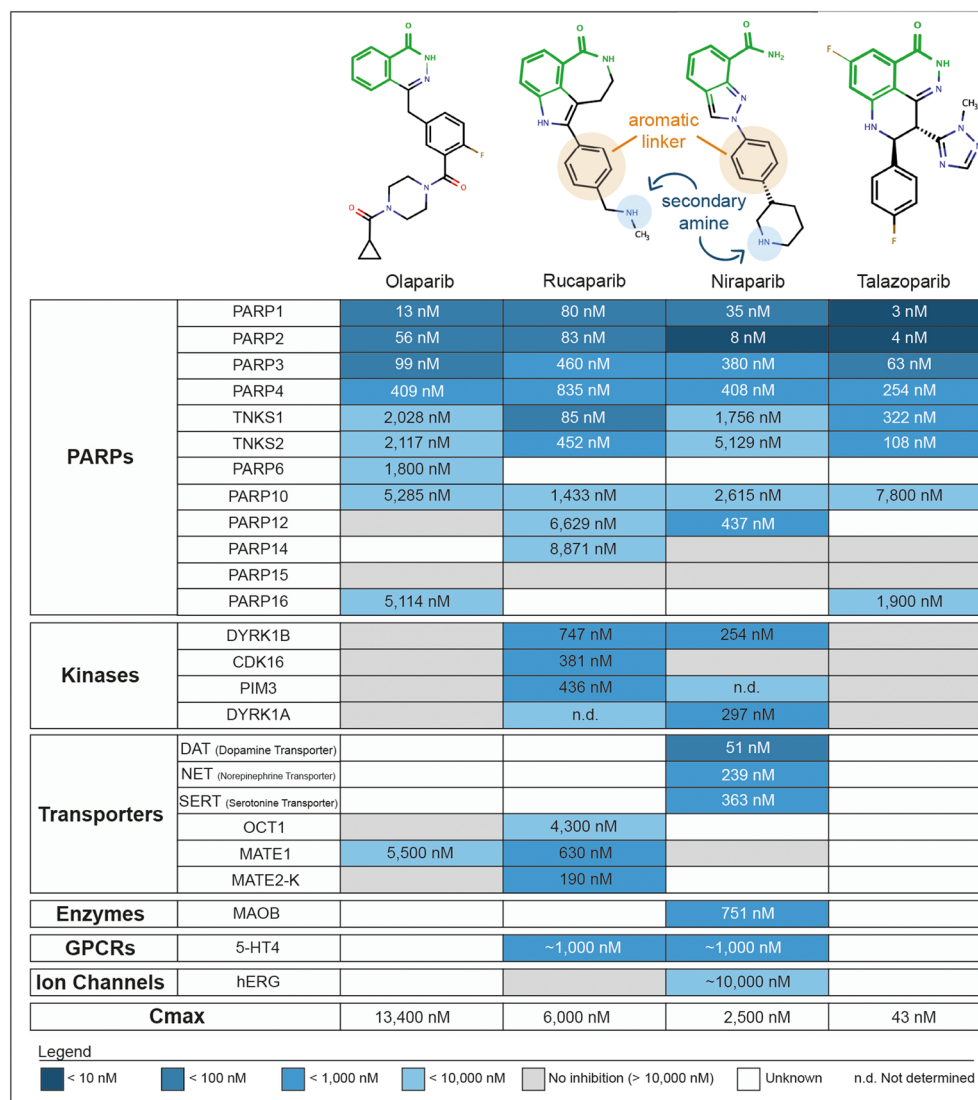
## 2.5 | Statistical analysis

Chi-squared ( $\chi^2$ ) tests were performed on the standardised ADR/100000  $R_x$  data to determine statistically significant differences between the suspected ADRs and PARPi. A  $P$ -value of  $<.001$  was set for statistical significance using Excel for Microsoft 365 (Table S1). As this exploratory study focused on: (1) differences between the PARPi and not whether a particular ADR is related to PARPi therapy and (2) because of the exploratory nature of this study, the lack of data on potential confounders, and the relatively low incidence of some of the ADRs (and low prescribing numbers), disproportionate analysis and corrections for multiple comparisons were not used.

**TABLE 1** Physiochemical, blood–brain barrier, pharmacokinetic and pharmacological properties of the four PARPi

Variable	Olaparib	Rucaparib	Niraparib	Talazoparib	
<b>Molecular obesity and on-target efficiency metrics</b>					
$clog_{10}P$	1.96	2.45	2.47	2.11	
PARP1 $pIC_{50}$	7.90	7.10	7.46	8.55	
LLE	5.94	4.65	4.99	6.44	
<b>Blood–brain barrier penetrant properties</b>					
MW (Da)	434.47	323.37	320.40	380.36	
$pK_a$	Neutral	Base: 9.32	Base: 10.08	Neutral	
tPSA (Å)	86.37	56.92	72.94	88.49	
HB acceptors	4	2	4	6	
HB donors	1	3	2	2	
$\log D_{7.4}$	1.96	0.55	−0.11	2.11	
P-glycoprotein substrate	Yes	Yes	Yes	Yes	
No. of BBB requirements met	6	4	3	4	
<b>Pharmacokinetics</b>					
Bioavailability	–	–	36%	73%	41%
Half-life (h)	(T) 15	(C) 11.9	25.9	48–51	90
$T_{max}$ (h)	(T) 1.5	(C) 1–3	1.9	3	1–2
$C_{max}$ (nM)	13 400	6000	2500	2500	43
Hepatic metabolism	Yes: CYP3A4	Yes: CYP2D6	Yes: carboxylesterases	No	No
Renal excretion	44%	17.4%	47.5%	68%	68%
Volume of distribution (L)	(T) 158	(C) 167	420	1074	420
Clearance (L/h)	(T) 7	(C) 8.6	6.5	16.2	6.5
PPB	82%	70.2%	83%	74%	74%
Dosing	BID (300 mg)	BID (600 mg)	OD (300 mg)	OD (1 mg)	OD (1 mg)

Abbreviations: (C), capsule formulation;  $clog D_{7.4}$ , calculated  $\log_{10}D$  at pH 7.4;  $clog_{10}P$ , calculated  $\log_{10}P$ ; HB, hydrogen bond; MW, molecular weight; LLE, lipophilic ligand efficiency;  $pIC_{50}$ ,  $-\log_{10}$  (half maximum inhibitory concentration);  $pK_a$ , acid dissociation constant; PPB, plasma protein binding; (T), tablet formulation;  $C_{max}$ , peak serum concentration;  $T_{max}$ , time taken to reach  $C_{max}$ ; tPSA, total polar surface area.



**FIGURE 1** Chemical structures of the four PARPi. The benzamide pharmacophore shared between the PARPi is highlighted in green. The bottom table shows the target selectivity profile of the four PARPi (median IC<sub>50</sub> values in nM)

## 2.6 | Ethics approval

The study used anonymised patient data and does not require ethical approval.

## 3 | RESULTS

### 3.1 | Chemical properties and pharmacokinetics

Properties of the PARPi relating to PARP1 inhibition (log<sub>10</sub>P, median pIC<sub>50</sub> and LLE) are shown in Table 1.

Niraparib was the most lipophilic drug studied (clog<sub>10</sub>P = 2.27). Talazoparib was the most potent for PARP1 (pIC<sub>50</sub> = 8.55). Rucaparib and niraparib both had an LLE below 5 (4.65 and 4.99, respectively).

Properties relevant to the risk of BBB penetration are shown in Table 1. All the PARPi met the molecular weight (MW) requirement: olaparib was the heaviest drug (434.47 Da). All the PARPi are basic or neutral, and all have a tPSA <90 Å, meeting

the requirements. Talazoparib failed to meet the hydrogen bond (HB) acceptor requirement (at 6 HB acceptors). Olaparib met the <2 HB donor requirement. Olaparib and talazoparib met the logD<sub>7.4</sub> requirement. All PARPi are P-glycoprotein (PgP) substrates; therefore, they do not meet this requirement but this PgP function declines with age. In summary, olaparib had the most BBB penetrant properties (six out of seven), followed by talazoparib and rucaparib (both four out of seven) and lastly niraparib (three out of seven). These results agree with published evidence of low BBB penetration and activity of PARPi in glioblastoma animal models, in part due to PgP.<sup>43</sup> Niraparib appears to have greater BBB penetration than olaparib, rucaparib or talazoparib<sup>44,45</sup> and has shown efficacy in brain metastasis.<sup>46</sup>

Niraparib had the largest volume of distribution (V<sub>d</sub>) at 1074 L, followed by talazoparib (420 L), rucaparib (262–113 L) and olaparib (167–158 L). Talazoparib is the only PARPi that does not undergo hepatic metabolism and had the longest half-life (90 h),<sup>47</sup> whereas olaparib had the shortest (15–11.9 h). The differences in behaviour of the tablet and capsule formulation of olaparib affects half-life and clearance.<sup>48</sup>

### 3.2 | Target affinity

The polypharmacology profiles of the PARPi are shown in Figure 1. This represents the most complete picture of the polypharmacology of PARPi to date, facilitated by the integration of several information sources spanning six different target families (PARPs, kinases, transporters, GPCRs, enzymes and ion channels).<sup>49</sup> The data on the inhibition of transporters has been largely overlooked to date.

Talazoparib was most potent towards PARP1 (3 nM) and PARP2 (4 nM) and had the lowest number of off-target effects ( $n = 6$ ). Rucaparib was the least selective PARPi in a recent kinome profiling,<sup>14</sup> possessing off-target activity on kinases ( $n = 12$ ), three in the nanomolar range, and was least potent towards PARP1 (80 nM) and PARP2 (83 nM). Niraparib had a distinct kinase polypharmacology profile to rucaparib, a unique inhibition of dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) and interacts with various neurotransmitter transporters (Figure 1).<sup>38</sup> Rucaparib and niraparib have the least clean profiles.

### 3.3 | Total general ADRs and fatalities

To support the use of all suspected ADR data since launch to generate the ADR rate/100000  $R_x$ , the comparison of suspected ADRs to  $R_x$  for the period 1 January 2019–7 July 2020 gave analogous trends (Figure S4 in the Supporting Information). Table 2 shows the following general trend: rucaparib had the highest number of reported ADRs per 100 000  $R_x$  (8898.31) followed by talazoparib (5319.15), niraparib (4004.77) and olaparib (1696.55). Rucaparib also reported the highest number of suspected fatalities per 100 000  $R_x$  (529.66) followed by olaparib (82.76). Niraparib and talazoparib are both yet to report any suspected fatalities associated with usage.

### 3.4 | Blood/lymphatic system ADRs and fatalities

Blood/lymphatic system ADRs followed the general ADR reporting trend, with rucaparib having the highest rate of ADRs, with 1218.22 (per 100 000  $R_x$ ). Talazoparib had the highest number of thrombocytopenia reports at 1063.83 per 100 000  $R_x$ .

### 3.5 | Vascular ADRs and fatalities

Talazoparib had the most suspected vascular ADRs at 2127.66 per 100 000  $R_x$  (Table 2). Talazoparib, rucaparib and olaparib all had reports of hypotension (1063.83, 52.97 and 13.39 per 100 000  $R_x$ , respectively). Niraparib had no reported cases of hypotension; instead, it was the only PARPi to exhibit hypertension (102.25 per 100 000  $R_x$ ).

### 3.6 | Cardiac ADRs and fatalities

Rucaparib had the highest number of cardiac ADRs at 211.86 per 100 000  $R_x$  (Table 2). Olaparib and talazoparib had no reported reactions. Rucaparib was the only PARPi to have a reported fatality with 52.97 suspected fatalities per 100 000  $R_x$ . Rucaparib also had the highest suspected rate of arrhythmias (105.93), followed by niraparib (68.17).

### 3.7 | Nervous/psychiatric ADRs

Niraparib exhibited several psychiatric ADRs compared to both olaparib and rucaparib (22 cases vs 1 case each, respectively, Table 2). These included: sleep disorders (8 cases), schizophrenia, deliria (both 3 cases), anxiety, mania/bipolar, general psychiatric disorders (all cases), depression, behavioural symptoms (both 1 case). With nervous system disorders, the following ADR trend emerged: niraparib > olaparib > rucaparib.

### 3.8 | Miscellaneous ADRs and fatalities

Rucaparib had the highest number of ADRs associated with infection/infestation, at 529.66 per 100 000  $R_x$  (Table 2). This is followed by niraparib (51.12) and olaparib (27.59). Talazoparib had no cases.

Gastrointestinal ADRs follow the general ADR trend with rucaparib having the highest number of ADRs (847.46) and fatalities (52.97). Rucaparib and niraparib both had reported cases of nausea/vomiting and constipation; rucaparib had the highest reports of vomiting/nausea (423.73), whereas niraparib had the highest reports of constipation (136.33).

Rucaparib had the highest number of ADRs linked to neoplasms (423.73). From Table 2, half of the reported fatalities associated with olaparib and rucaparib are due to neoplasms (41.38 and 264.83, respectively).

## 4 | DISCUSSION

### 4.1 | Total ADRs and fatalities

Based on the chemical properties (Table 1), rucaparib was predicted to have the greatest polypharmacology as it had the lowest LLE (4.65). This proved to be the case. Rucaparib showed pan-PARPi activity, with poor selectivity for the main biological targets and several significant off-target effects (Figure 1). Rucaparib also had the most reported ADRs and the highest reporting rate of fatalities. This implied the severity and frequency of ADRs is greatest with rucaparib out of the four PARPi.

Talazoparib was licensed in 2019, which explains the low level of prescriptions (Figure S1) and ADRs; this likely skewed the data, thus

**TABLE 2** Summary of the reported ADRs within the UK, associated with the four PARPi

	Olaparib	Rucaparib	Niraparib	Talazoparib	P-value
Total prescriptions <sup>a</sup>	7250	1888	5868	94	
Total ADRs	132 (1696.55)	168 (8898.31)	235 (4004.77)	5 (5319.15)	<.001
Fatalities	6 (82.76)	10 (529.66)	0	0	<.001
<b>Blood and lymphatic system</b>					
Total ADRs	11 (151.72)	23 (1218.22)	42 (715.75)	1 (1063.83)	<.001
Fatalities	0	0	0	0	–
Thrombocytopenia	2 (27.59)	5 (264.83)	24 (408.96)	1 (1063.83)	<.001
<b>Vascular disorders</b>					
Total ADRs	1 (13.79)	1 (52.97)	8 (136.33)	2 (2127.66)	<.001
Fatalities	0	0	0	0	–
Hypotension	1 (13.79)	1 (52.97)	0	1 (1063.83)	<.001
Hypertension	0	0	6 (102.25)	0	<.001
<b>Cardiac disorders</b>					
Total ADRs	0	4 (211.86)	6 (102.25)	0	<.001
Fatalities	0	1 (52.97)	0	0	<.001
Arrhythmias	0	2 (105.93)	4 (68.17)	0	<.001
<b>Infections and infestations</b>					
Total ADRs	2 (27.59)	10 (529.66)	3 (51.12)	0	<.001
Fatalities	0	0	0	0	–
<b>Gastrointestinal disorders</b>					
Total ADRs	3 (41.38)	16 (847.46)	27 (460.12)	0	<.001
Fatalities	0	1 (52.97)	0	0	<.001
Nausea/vomiting	0	8 (423.73)	7 (119.29)	0	<.001
Constipation	0	1 (52.97)	8 (136.33)	0	<.001
<b>Neoplasms benign or malignant</b>					
Total ADRs	13 (179.31)	8 (423.73)	10 (170.42)	0	<.001
Fatalities	3 (41.38)	5 (264.83)	0	0	<.001
<b>Nervous system</b>					
	9 (124)	4 (212)	18 (307)	0	<.001
<b>Psychiatric disorders</b>					
	1 (14)	1 (53)	22 (375)	0	<.001

<sup>a</sup>Formulae were used to estimate the total number of prescriptions from the total number of items dispensed between January 2019 and July 2020. Numbers in parentheses are reported ADRs per 100 000  $R_x$ . *P*-values were obtained by chi-squared analysis. *P*-values included are derived from the chi-squared test analysis of all four PARPi. Some *P*-values contain a dash (–) as a *P*-value could not be calculated.

the data for talazoparib was excluded from discussions that drew a conclusion as to risk. Rucaparib, niraparib and talazoparib are all black triangle drugs and all suspected ADRs need to be reported regardless of severity. There is likely to be a significant under-reporting of suspected ADRs.<sup>50,51</sup>

## 4.2 | Blood/lymphatic system ADRs and fatalities

The results show that all PARPi had reported cases of ADRs related to the blood/lymphatic system (Table 2). This is indicative of a class effect due to their mechanism of action. Thrombocytopenia is associated with a reversible decrease in megakaryocyte proliferation and maturation.<sup>52,53</sup> Exposure to bone marrow is determined by the volume of distribution ( $V_d$ ) of a drug, with a

higher  $V_d$  leading to increased distribution into bone marrow.<sup>54</sup> Niraparib has a  $V_d$  of 1074 L, significantly higher than talazoparib (420 L), so would be expected to have a higher number of cases.<sup>15</sup> Talazoparib has a higher proportion of thrombocytopenia-related ADRs (1063.83 per 100 000  $R_x$ ), which could be attributable to its higher PARP-trapping—an effect identified as driving bone marrow toxicity.<sup>55</sup> However, caution must be excised given the significantly smaller number of prescriptions for talazoparib. This research indicates a potential link between  $V_d$  and thrombocytopenia, balanced by the trapping potential of each PARPi. Niraparib had a significantly higher number of thrombocytopenia cases ( $P < .001$ ) compared to rucaparib and olaparib (Table S1 in the Supporting Information). This was supported by LaFargue et al.<sup>15</sup> who showed thrombocytopenia was more pronounced with niraparib (61% of 367 patients).

### 4.3 | Vascular ADRs and fatalities

Niraparib was the only PARPi to have reported cases of hypertension (102.25 per 100 000 R<sub>x</sub>)—an established side effect to niraparib<sup>56</sup>—whereas the other PARPi had cases of hypotension. It has been hypothesised that hypertension might be produced due to an off-target disruption of dopamine<sup>57</sup> and noradrenaline metabolism via the inhibition of **DAT** (dopamine transporter), **NET** (norepinephrine transporter) and **SERT** (serotonin transporter) by niraparib (Figure 1).<sup>15</sup> Despite the complexity associated with blocking several transporters and its potential opposing effects on blood pressure, it remains a plausible hypothesis.<sup>58</sup> The unique inhibition of DYRK1A (IC<sub>50</sub> = 297 nM vs C<sub>max</sub> 2500 nM) by niraparib could also contribute to the hypertension reported. DYRK1A has been suggested to be involved in the turnover of these neurotransmitters, with studies showing a strong relationship between DYRK1A level and the dopaminergic system.<sup>59</sup> Overexpression of DYRK1A reduces levels of dopamine, serotonin and noradrenaline in certain areas of the brain.<sup>59</sup> As niraparib inhibits DYRK1A, increased levels of these neurotransmitters would be seen, which in turn have inotropic effects on the heart, causing high blood pressure. DYRK1A also has a role in circadian rhythm. DYRK1A has been shown to be a novel clock component, cooperating with GSK-3β, and governing the Ser557 phosphorylation-triggered degradation of cryptochrome-2 (CRY2).<sup>60</sup> As blood pressure exhibits a circadian rhythm,<sup>61</sup> disruption may potentially cause hypertension. These results could be important for the selection of PARPi for hypertensive patients.

### 4.4 | Cardiac ADRs and fatalities

Niraparib and rucaparib were the only PARPi to have cases of cardiac ADRs but the difference in the number of cases was not significant ( $P = .004$ ). These drugs share similar structural features. Arrhythmia is not an established side effect of rucaparib or niraparib.<sup>56</sup>

Inhibition of the K<sub>v</sub>11.1 (**hERG**) potassium ion channel causes QT prolongation resulting in arrhythmia known as *torsades de pointes*.<sup>62</sup> Niraparib and rucaparib are both weak, basic drug molecules, known features of potential hERG inhibitors (Figure 1).<sup>63,64</sup> In contrast, olaparib and talazoparib had no reported cases of arrhythmia and do not contain these structural features, which may explain why arrhythmia cases are, so far, unique to niraparib and rucaparib.

Segan et al. found that the IC<sub>50</sub> of rucaparib against the hERG channel (IC<sub>50</sub> = 22.6 μM) is 13-fold higher than the peak serum concentration, concluding significant potency of rucaparib against hERG in patients with pre-existing long QT.<sup>65</sup>

Our interpretation of this differs (it is only ~four fold higher). Thus, hERG IC<sub>50</sub> is not clinically achievable based on comparison of the IC<sub>50</sub>s, as rucaparib's C<sub>max</sub> is 6 μM. A modest inhibitory effect on hERG could potentially occur. Comparing in vitro and in vivo pharmacology can be complicated by accumulation and efflux events in vivo, which may modulate the potency for hERG in man.

### 4.5 | Nervous/psychiatric ADRs

The disparity in psychiatric ADRs with niraparib vs olaparib/rucaparib (Table 2) may be related to niraparib's pan-neurotransmitter pharmacology (Figure 1). All are at clinically achievable concentrations, in particular DAT inhibition is 51 nM (C<sub>max</sub> = 2.5 μM). These neurotransmitters could be involved in the sleep disorders that are the most common disorder observed with niraparib.<sup>66</sup> Dopamine also has a clear role in schizophrenia and deliria, the second and third most observed psychiatric ADRs.<sup>66</sup> However, niraparib has the least number of BBB penetrant properties and has been shown to have reduced BBB penetration,<sup>67,68</sup> which may mitigate this risk.

Nervous system disorders also emerged as a potential ADR for niraparib. A definitive link could not be drawn due to incomplete reporting of all off-target profiles of PARPi. However, off-target inhibition of the **5-HT<sub>4</sub>** receptor may warrant further investigation.<sup>69</sup>

### 4.6 | Miscellaneous ADRs and fatalities

PARPi can have a neutropenic effect, although the mechanism is not completely understood. Neutropenia was the third most common haematological toxicity observed in phase III trials. Assessment of the efficacy and safety of PARPi in BRCA-positive ovarian patients found that neutropenia occurred in 30% of all patients treated with niraparib, 19% of people treated with olaparib and 18% of people treated with rucaparib.<sup>70</sup> Neutropenia leads to increased risk of infection.<sup>15</sup>

Gastrointestinal toxicities are mediated via off-target kinase inhibition. These types of ADRs (e.g. vomiting) are common for kinase inhibitors.<sup>71</sup> Other studies have shown vomiting and nausea are most prevalent in rucaparib, at 76% and 37% of patients respectively, with constipation being most prevalent in niraparib (40%).<sup>15</sup>

PARPi are associated with hypercholesterolaemia and hypertransaminasemia. Rucaparib increased cholesterol levels of any grade in 40–84% of patients; nevertheless, serious ADRs of grade 3/4 hypercholesterolaemia were only reported in 2–4% of patients. There are also reports for elevation of alanine aminotransferase 1 (ALT) and aspartate aminotransferase (AST) in 36% and 28% of patients treated with niraparib, respectively. Olaparib is better tolerated with reported incidences of increased ALT and AST of 5% and 2%, respectively. PARPi may also elevate creatinine concentrations; this might not affect the glomerular filtration rate or lead to renal failure. Rucaparib inhibits kidney transporter proteins multidrug and toxin extrusion (MATE1) and MATE2 (multidrug and toxin extrusion protein 2, MATE2-K), which affect the secretion of creatinine, whilst niraparib does not inhibit MATE1 and is not related to elevated serum creatinine.<sup>72,73</sup> Olaparib also inhibits MATE1 with IC<sub>50</sub> < 10 μM and is also associated with elevated creatinine levels.<sup>74,75</sup>



## 4.7 | Limitations

The Interactive Drug Analysis Profiles, from the MHRA, give a complete listing of all the spontaneous suspected ADRs reported through the Yellow Card scheme. While essential to safety monitoring, spontaneous reporting schemes have several inherent weaknesses. It is estimated that only 6% of ADRs are reported to regulatory authorities,<sup>50</sup> which may lead to the underestimation of any given ADR. Under-reporting may vary by both reaction and by drug, even within the same class. Publicity about an adverse effect,<sup>76</sup> length of time on the market, and novelty of the drug (such as the first-in-class) may also affect reporting. This can mean that comparisons between drugs using such reports can be problematic, particularly when small numbers are involved. In our study, this is particularly seen with talazoparib, where a single report can lead to a reporting rate of 1063 per 100 000 R<sub>x</sub>. Declines in reporting ADRs after the second year a drug has been on the market, known as the Weber effect, have been reported, although it has been documented that reporting rates in oncology drugs are inconsistent and not in line with the Weber effect.<sup>77</sup>

Reporters are requested to report any suspected ADRs, and they do not have to demonstrate a clear causal link with the drug. This means that many reported ADRs may not be linked to the drug. Care needs to be taken with suspected fatal cases, where reporters may be more likely to err on the side of reporting due to the seriousness of the reaction. Confounding may also occur from previous exposure to platinum-based therapy, or concomitant disease, either causing or contributing towards the reported ADR. Therefore, conclusions on the safety and risks of medicines cannot be made on the information obtained from the Drug Analysis Profiles alone. However, such data can be useful for hypothesis generation as in this study and supported by primary literature reports and case studies.

Secondary Care Medicines data was available from January 2019 and considered the total number of items processed in each NHS organisation within England. A comprehensive summary of how these drugs have been prescribed since their license date was not possible and will be required for longer term research into PARPi. Prescribing guidelines have changed since the first PARPi launched which will affect their usage longitudinally. As the data considered the total number of items processed, prescribing data had to be estimated. This is not an accurate representation of the true prescribing numbers. Chemotherapy is highly patient specific. This will impact our estimation as the standard dose was used to calculate the number of prescriptions which may have deviated from the true value.

Differences between PARPi include chemical structure, preclinical potency and dose regimen. Differences in size and rigidity are hypothesised to be the basis for the distinct behaviour of each PARPi to prevent the release of bound PARP1/2 from chromatin. This is associated with high myelosuppression, which results in variation of the recommended doses across PARPi.<sup>78</sup>

The available data on the polypharmacology of PARPi is incomplete.<sup>79,80</sup> In this work, we have mitigated this risk by performing data integration of the pharmacological effects of PARPi, integrating public databases, literature and NDA documentation. However, not all PARPi

had been comprehensively tested against all the targets we identified and their interactions with other target families remains unknown.

## 5 | CONCLUSIONS

The emergence of PARPi have revolutionised the treatment of several cancer types. Therefore, it is essential that we understand the polypharmacology and safety of these drugs.

This study has demonstrated that PARPi have clinically significantly different suspected ADRs reported to the Yellow Card scheme which may be tentatively linked to their unique pharmacological profiles. Established ADRs have a clear pharmacological relationship to either the structure of the drug or polypharmacology. Our results illustrate that, despite having the same mechanism of action, the safety profile based on spontaneously reported data of PARPi varies.

The research reinforced current knowledge, for example the link between V<sub>α</sub> and thrombocytopenia.

The research provided new insight into why certain ADRs occur, such as DYRK1A inhibition and hypertension. Further research is still required; currently, prescribing numbers of these drugs are low, as is the number of reported ADRs, and so is the power of this study. Based on these conclusions, in the short term, clinicians should be aware of the safety profile of these drugs and the potential contraindications. Prescribing rates are on the rise for PARPi, therefore it is important to identify patients who may benefit from closer monitoring.

## 6 | NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.<sup>40-42</sup>

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### COMPETING INTERESTS

A.A.A. is an employee and A.M.J. has previously been an employee of The Institute of Cancer Research (ICR), which has a commercial interest in a range of drug targets, including PARP inhibitors. The authors who are, or have been, employed by The Institute of Cancer Research are subject to a "Rewards for Inventors Scheme", which may reward contributors to a program that is subsequently licensed. A.A.A. has been instrumental in the creation/development of canSAR and Probe

Miner. A.R.C. is an honorary pharmacovigilance pharmacist at the West Midlands Yellow Card Centre.

## CONTRIBUTORS

D.S. carried out the data acquisition, analysis and interpretation, and drafted and revised the manuscript. A.A.A. carried out data analysis and interpretation, and drafted and revised the manuscript. A.R.C. carried out data interpretation and revised the manuscript. A.M.J. conceived and designed the study including analysis and interpretation of data for the work, and supervised, drafted and revised the manuscript. All authors gave final approval to the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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