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Title

**Comparative Study on the Occurrence of Adverse Effects in the Concomitant Use of Azathioprine
and Aldehyde Oxidase Inhibitors**

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Authors' contributions

HU, KN and MK designed the study. HU and SA performed data curation and formal analyses.

All authors contributed to the data interpretation. HU drafted the manuscript. KN supervised the study. All
authors contributed to the critical revision of the manuscript for important intellectual content.

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Comparative Study on the Occurrence of Adverse Effects in the Concomitant Use of Azathioprine and Aldehyde Oxidase Inhibitors

Abstract

Objectives: Aldehyde oxidase (AO) is a molybdenum-containing redox enzyme similar to xanthine oxidase that is involved in the thiopurine metabolism. This study investigated the effects of drug-drug interactions (DDIs) between azathioprine (AZA) and AO inhibitors on hematologic and hepatic disorders using the U.S. Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report database.

Methods: The presence of DDI was assessed using the interaction signal scores (ISSs) calculated via the reporting odds ratios and 95% confidence intervals. The study used reports of "azathioprine" as a suspect drug for adverse effects. AO inhibitors were selected based on previous *in vitro* reports.

Results: Some drugs tested positive for ISSs in each database and type of adverse effect (hematologic or hepatic disorder) analysis. Among these drugs, chlorpromazine, clozapine, hydralazine, and quetiapine could inhibit AZA metabolism via AO, given the previously reported clinical blood concentration and inhibitory effects of each drug.

19

20 **Conclusion:** Concomitant use of AO inhibitors increased the signals for AZA-induced adverse effects. To
21 date, no studies have evaluated the clinical importance of AO as a drug-metabolizing enzyme, and further
22 *in vitro* and clinical research is needed to clarify the contribution of AO to the pharmacokinetics of
23 thiopurines.

24

25 **Key words:** Aldehyde oxidase, azathioprine, FAERS, JADER, hematologic disorders, data mining signal
26 detection

1. Introduction

Azathioprine (AZA) is an immunosuppressive drug that is used to treat inflammatory bowel disease and systemic lupus erythematosus [1]. 6-Mercaptopurine (6-MP), which is metabolized and initially produced from AZA, can be metabolized by multiple enzymatic reactions: 1) phosphorylation to the active substances, 6-thioguanine nucleotides (6-TGNs), 2) methylation to 6-methyl mercaptopurine ribonucleotides (6-MMP) by thiopurine methyltransferase (TPMT), and 3) oxidation to 6-thiouric acid (6-TUA) by some molybdenum enzymes such as aldehyde oxidase (AO) and xanthine oxidase (XO) (Fig.1). The relative activity and quantity of each enzyme determine the amount of metabolites produced.

The major reason for stopping AZA treatment is adverse effects [2, 3]. Hematological and hepatological toxicities are representative AZA-induced adverse effects, and these harmful events are proportional to the blood concentration of AZA metabolites. 6-TGNs are the main active metabolites with immunosuppressive effects and an increase in their concentration induces pancytopenia [4, 5]. Although 6-MMP is an inactive compound, there have been reports of a correlation between its blood levels and liver injury [6]. Therefore, contributions of the metabolic enzymes must be considered while prescribing AZA to abate its adverse effects. Several clinical trials have shown that approximately 20–50% of patients using thiopurine preparations do not receive effective treatment because of the skewed thiopurine metabolism [7, 8]. Polymorphisms in metabolic enzymes such as TPMT and nudix hydrolase 15 can influence the therapeutic and adverse effects of AZA treatment [9-12]. Although the evaluation of these enzyme activities

is useful for predicting the pharmacokinetics of AZA, it alone cannot explain the amount of metabolites or the development of myelotoxicity [7]. Hence, more detailed information on the metabolic enzymes is required to provide appropriate thiopurine therapy because of the complex metabolic pathways involved.

AO is a redox enzyme that is primarily located in the hepatic cytosol. This enzyme is classified as a molybdenum-containing enzyme, such as XO, but has broader compound recognition, including aldehyde-containing or N-containing heterocyclic drugs and internal substrates [13]. 6-MP is also metabolized via 6-thioxanthine (6-TX) to 6-TUA, which is associated with both XO and AO. There are species differences in the oxidation of 6-MP; AO is involved in the oxidation of 6-MP to 6-TX in the human liver cytosol, whereas 6-TX is converted to 6-TUA in guinea pigs [14, 15]. As the formation of 6-TX is the first step in 6-MP metabolism, AO may be one of the factors that determines the production of 6-MP metabolites in humans. Clinical trials have reported that the AO polymorphism N1135S (rs55754655) may result in reduced AZA treatment efficacy [16, 17]. However, the effect of AO on AZA treatment and incidence of adverse effects remain limited.

The inhibition of AO activity by various drugs has been studied using extracts of the liver cytosol or AO expressed cells [18]. Although this enzyme can cause drug-drug interactions (DDIs), little is known about the clinical impact of AO inhibitors on the therapeutic efficacy or toxicity of drugs metabolized by AO. Therefore, it is important to determine the effects of AO inhibitors on AZA-induced adverse effects and pharmacokinetics. In this study, we examined AO-mediated DDIs using real-world adverse event

63 databases, such as the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and
64 the Japanese Adverse Drug Event Report database (JADER).

2. Materials & Methods

2.1. Study Design

We downloaded FAERS and JADER, adverse event reporting databases provided by the FDA and PMDA, respectively. The time period selected for the analysis were July 2014 to December 2021 for FAERS and April 2004 to March 2022 for JADER. The FAERS database consists of quarterly data and duplicate reports. Therefore, duplicates were removed based on the ID assigned to each report, and only the latest report was used for analysis. The reported cases recommended for deletion by the FDA were removed based on the deleted files. Adverse events caused by AZA were identified in reports that included "azathioprine" in the product active ingredient column, and hepatic and hematologic disorders were defined by preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) ver. 25.0 included in drug-related hepatic disorders (SMQ; Standardized MedDRA Queries code:20000006) or hematopoietic cytopenias (SMQ:20000027). Drugs that can inhibit AO were selected based on previous studies [18]. Additionally, "AO inhibitors" were defined as drugs meeting the following criteria in this study: 1) must be approved by the FDA or the Japanese Ministry of Health, Labour and Welfare (MHLW), 2) must not be a bioactive substance, 3) must be administered orally or intravenously and not intended for topical action, 4) must remain on the market as of March 2023, and 5) must have a sufficient number of reports to calculate the signals when used with azathioprine. Drugs suspected as the cause of adverse effects were included with the role code as "PS; Primary Suspect drug" and "SS; Secondary Suspect drug". Drugs administered

through trans-mammary or -placental routes were excluded.

2.2. Statistical Analysis

The disproportionate number of adverse effect reports was analyzed using reporting odds ratio (ROR) and corresponding 95% confidence intervals (95% CI) [19]. The interaction signal score (ISS) was used to evaluate DDIs in this study. ISS was defined as positive when the following conditions were applied: 1) number of reports for each used in the ROR calculation > 3 reports, 2) ROR of concomitant use of AZA and AO-inhibiting drugs ($ROR_{AZA \cap AO \text{ inhibitor}} > 1$, and 3) lower limit of the $ROR_{AZA \cap AO \text{ inhibitor}}$ exceeded the upper limit of the ROR when each drug was used alone (ROR_{AZA} and $ROR_{AO \text{ inhibitor}}$). The ISS was defined as described in previous reports, and a lower limit was set based on the number of reports to provide a conservative model [20–22].

The Ω shrinkage measure model, a more conservative model used by the WHO Uppsala Monitoring Center (WHO-UMC), was used as a supplement to analyze the FAERS database and evaluate the DDIs [21, 23]. We calculated Ω as reported in previous studies and obtained Ω_{025} , assuming it follows a standard normal distribution [21, 22]. As reported previously, an interaction was defined as positive if $\Omega_{025} > 0$, the lower limit of 95% CI of Ω exceeds zero. The details of the calculations are described in Equations (1)–(3).

$$\Omega = \log_2 \frac{n_{111} + 0.5}{E_{111} + 0.5} \quad (1)$$

$$\text{Var}(\Omega_0) = \text{Var}\left(\log_2 \frac{n_{111}}{E_{111}}\right) \approx \frac{1}{n_{111} + \log(2)^2} \quad (2)$$

$$\Omega_{025} = \Omega - \frac{\phi(0.975)}{\log(2)\sqrt{n_{111}}} \quad (3)$$

where n_{111} is the number of adverse events caused by AZA and AO inhibitors, and E_{111} is the expected value.

$\phi(0.975)$ is 97.5% of the standard normal distribution. All statistical analyses were conducted using R

software (ver 4.2.3).

3. Results

3.1. Hematologic disorders

A total of 98,419 and 4,713 reports of AZA marked as a suspected drug for adverse effects were found in the FAERS and JADER databases, respectively. In FAERS, the ROR [95% CI] of the hematologic disorders including AZA as a suspected drug was 1.81 [1.75 – 1.87]. The RORs for the combination of AZA and each drug are shown in Figure 2. Positive ISSs for hematologic disorders were determined that occurred concomitantly with the use of amlodipine (ROR: 3.26 [95% CI: 2.72 – 3.91]), chlorpromazine (47.92 [26.35 – 87.14]), clozapine (15.69 [10.73 – 22.93]), cyclobenzaprine (5.07 [3.48 – 7.38]), felodipine (4.16 [2.88 – 6.00]), hydralazine (6.28 [3.60 – 10.94]), loratadine (4.15 [2.63 – 6.55]), metoclopramide (3.59 [2.70 – 4.76]), olanzapine (13.80 [9.54 – 19.95]), ondansetron (2.61 [2.01 – 3.39]), and quetiapine (5.70 [4.40 – 7.38]). Using the Ω shrinkage measure model, signals for the following combinations were detected: amlodipine (Ω_{025} : 0.58), chlorpromazine (2.82), clozapine (0.25), cyclobenzaprine (0.86), felodipine (0.61), hydralazine (0.82), loratadine (0.47), metoclopramide (0.54), olanzapine (1.99), and quetiapine (1.20) (Table S1). In JADER, the RORs for AZA was 2.77 [2.59 – 2.97], and the ISS was determined as positive for the combination with amlodipine (5.21 [3.64 – 7.47]) (Fig. 3). The drugs not listed in Figure 3 could not be subjected to disproportionality analysis because of the small number of reported cases when used in combination with AZA.

3.2. Hepatic disorders

In the FAERS database, ROR of hepatic disorders, including AZA as a suspected drug was 2.28 [2.20 – 2.36] (Fig. 4). Clozapine (5.67 [3.07 – 10.48]) and ondansetron (7.90 [6.54 – 9.53]) were only determined as disproportionate with the ISSs for hepatic disorders. With the Ω shrinkage measure model, same two drugs were detected as signal: clozapine (Ω_{025} : 0.32) and ondansetron (1.23) (Table S2). Although none of the ISSs were detected in the JADER database, the ROR for AZA was 1.25 [1.11 – 1.40], with the highest ROR of 5.33 [1.74 – 16.35] when used with hydralazine (Fig. 5).

4. Discussion

AO plays an important role in drug metabolism because of its broad substrate specificity. Currently, drug labeling describes the co-administration of zaleplon, a non-benzodiazepine hypnotic that is a substrate of AO, and cimetidine, which can inhibit AO, to increase the blood levels of zaleplon. This is the only report of AO-mediated interactions in clinical research. Metabolites of zaleplon are known to get reduced by AO inhibitors such as chlorpromazine, hydralazine, promethazine, and menadione, as evaluated *in vitro* using human liver slices [24, 25]. Reports on the pharmacokinetics and pharmacogenomics of anticancer drugs metabolized by AO also suggest an important role for AO as a drug-metabolizing enzyme [26-28]. However, the clinical significance of AO is less well-studied than that of the cytochrome P450 enzymes.

Clinical studies revealing that AO polymorphisms are associated with AZA treatment indicate that AO plays an important role in the AZA metabolic pathway [16, 17]. Metabolic studies of 6-MP in human liver cytosol have reported that AO contributes to oxidative reactions similar to XO, and the contribution of AO in this oxidative pathway is estimated to be approximately 30–40 % based on this *in vitro* study [14]. Inhibition of XO is known to increase 6-MMP and 6-TGN because of the relative increase in the proportion of metabolism by TPMT and hypoxanthine guanine phosphoribosyl transferase. Allopurinol, an XO inhibitor, has been shown to increase the risk of hepatotoxicity and hematologic toxicity of AZA *in vitro* and in clinical studies [29]. Therefore, inhibition of AO, as well as inhibition against XO,

could also increase the risk of AZA adverse effects. The association between AO activity and AZA dosage should be actively confirmed as genotyping for AZA-metabolizing enzymes and measuring AZA metabolites have been shown to reduce the risk of adverse reactions [30].

In this study, we used FAERS and JADER to examine whether drugs that inhibit AO alter the susceptibility of azathioprine to adverse effects. To evaluate DDIs in clinical pharmacokinetics, we calculated the ratio of inhibitor blood concentration ([I]) to inhibitory activity for AO (IC_{50}) as a measure of interaction (Table 1). The optimal value for [I] could be discussed either in the blood or hepatocytes, and since there is no difference in research methods, the maximum blood concentration (C_{max}) was adopted in this study [31]. Clinical C_{max} information was obtained from the drug inserts manufactured by each pharmaceutical company published by the MHLW; IC_{50} were based on previous *in vitro* studies using human liver cytosol [18]. In general, an [I]/ IC_{50} greater than 0.1 is considered that the risk of *in vivo* drug interactions should be investigated [32].

As shown in Table 1, the following drugs were considered as agents with inhibitory effects on AO that could contribute to drug interactions; raloxifene, chlorpromazine, clozapine, amitriptyline, quetiapine, and clomipramine. Hydralazine was not included in the table because it gets metabolized to phthalazine, which was incompatible with the phthalazine metabolism experiments in previous reports. However, hydralazine is known to inhibit AO even at clinical concentrations, as revealed by *in vivo* studies [33, 34]. Of the drugs listed above, ISSs for chlorpromazine, clozapine, quetiapine, and hydralazine were

positive for any of the adverse effects reported in the disequilibrium analyses (Fig. 2–5). There are limited reports involving AO inhibitors, such as raloxifene; thus, the ISSs for these drugs could be inaccurate.

Typically, competitive inhibitors are more important candidates for drug interactions than uncompetitive inhibitors because the effects of uncompetitive inhibitors are limited to the saturated state [35]. Chlorpromazine and clozapine are mixed competitive inhibitors but tend to exhibit relatively competitive behavior. The risk of drug interactions should be investigated based on the ratio of $[I]$ to K_i values, which represents the dissociation constant of the enzyme inhibitor complex ($[I]/K_i$: chlorpromazine, 0.8; clozapine, 0.4) [35]. Although raloxifene concentrations in the liver can reach K_i values, the effect of raloxifene is estimated to be small because it is a noncompetitive AO inhibitor [36]. However, it should be noted that the inhibition mode of raloxifene varies with the substrate [37]. The inhibition mechanisms of other AO inhibit drugs such as amitriptyline, quetiapine, and clomipramine have not been reported. Further studies on the inhibitory effects of these drugs on the oxidation of 6-MP or other substrates are required to assess their effects on thiopurine metabolism.

Amitriptyline did not alter the proportion of adverse event reports, although it inhibited AO at clinical concentrations. In the FAERS, some of the data included the dosage and administration of drugs. In reports that included AZA and amitriptyline, the percentage of reports using amitriptyline at a dose of 75 mg was higher in the group with hematologic disorders than in the group without (39.5% vs. 10.7%), whereas in other reports, the stated dose of amitriptyline in the group without blood damage was even lower

(data not shown). The $[I]/K_i$ values for amitriptyline were calculated at a concentration of 75 mg (Table 1); therefore, one would expect the inhibitory effect of AO to be even smaller at lower doses. However, due to the nature of systems reporting adverse events, this interpretation may not be correct, because the dosage information could be inaccurate or unknown.

There are drugs for which ISSs were positive despite low $[I]/K_i$ values. Although this study referred only to the effects of AO inhibition, AZA-induced hematologic and hepatic injury could be caused by various factors, such as the inhibition of TPMT, XO, and inosine monophosphate dehydrogenase [38, 39]. In addition to AO inhibition, these drugs could also affect the pharmacokinetic or pharmacodynamic profile of AZA in other ways. In addition, the number of drugs that tested positive for ISS was higher in patients with hematological disorders than in those with hepatic disorders. In combination with allopurinol, an improved response to thiopurine therapy and the development of adverse events have been reported via changes in the 6-MMP nucleotides/6-TG nucleotides ratio [40]. The mechanisms still remain unclear, however, there are some hypotheses regarding this alteration of the metabolite ratio, such as inhibition by AZA metabolites [41, 42]. This means that AO inhibition could cause an imbalance in the proportion of metabolites, resulting in a deviation in adverse effects.

We used two signal detection model referring ROR or Ω_{025} to screen DDIs in this study [19–22]. Although ROR calculation is easy, the scores tend to increase as the number of reports decreases. Thus, the $ROR_{drug1 \cap drug2}$ is often overestimated due to the small number of two-drug combination reports ($drug1 \cap$

drug2) than that of single-drug use reports (drug1 or drug2). In this study, ISS was defined as >3 reports, each used in the ROR calculation to reduce false-positive signals. As there is no definitive method for DDI analysis with an adverse drug reaction database, multiple algorithms should be used for good correlation. Therefore, signals from the ISS model based on ROR (Figures 2, 3) and Ω shrinkage measure model (Tables S1, S2), were detected for almost the same drug combinations. Previous studies have reported that Ω shrinkage measure model is more conservative for signal detection than frequency-based statistical scores such as ROR [22]. However, Ω is also overestimated when the target adverse effect is rare because of the decreased E_{III} . Qian et al. proposed that comparing the three models (logistic regression method, Ω shrinkage measure method, and additive and multiplicative models) would further help validate the results [43]. Further analysis using other algorithms dealing with signal detection and robust longitudinal observational studies are needed to reliably assess the potential interaction between AZA and AO inhibitors.

To date, the clinical significance of AO inhibitors has not been reported. To the best of our knowledge, this is the first study to evaluate the effects of AO inhibitors on AZA-induced adverse effects based on clinical reports. These results indicated that some drugs that inhibit AO could correlate with reports of the adverse hematologic and hepatic effects of AZA. However, it must be noted that this study had the following limitations. i) Incidence (rate of occurrence) could not be estimated solely from adverse event reporting systems. ii) These databases could not prove a causal relationship between the suspected drug and adverse events; they reflected only the observations and opinions of the reporters. iii) In these databases,

only information on adverse effects was aggregated; therefore, the impact on treatment efficacy could not be assessed. iv) These spontaneous reports often lacked accompanying information such as dosage, frequency, and length of the therapeutic period. v) Two adverse reaction databases, FAERS and JADER, were used in this study; however, because of differences in reporting rules and practices (e.g., in the U.S., pharmaceutical companies must submit non-severe adverse reactions, but not in Japan), the characteristics of their aggregated data are different [44]. In this study, the number of drugs that tested positive for ISSs was lower in the JADER than in the FAERS. The reasons could be social factors and differences in the healthcare systems in these databases as well as racial differences and the number of reports. These differences must be considered to comprehensively interpret the results obtained from these databases. vi) Although ISSs were decided positive when $ROR_{AZA \cap AO \text{ inhibitor}}$ exceeded both of ROR_{AZA} and $ROR_{AO \text{ inhibitor}}$ in this research, it could not be determined that there was a DDI, as some AO inhibitors were already known to be at risk for hematologic and hepatic disorders (e.g., clozapine-related neutropenia). In the future, the risk of AO inhibitors in the treatment of AZA should be clarified by clinical studies, and the mechanism of their effect on 6-MP metabolism should be clarified by *in vitro* studies.

5. Conclusion

Concomitant use of drugs presumed to inhibit AO at clinical blood concentrations increased the signals (ROR) for AZA-induced adverse effects. The association of DDIs between AZA and AO inhibitors

239 has not been previously reported. Further studies are necessary to determine the effects of this interaction
240 in AZA therapy.

241 **Disclosure statement**

242 The authors declare that they have no conflict of interest.

243

244 **Data availability**

245 The datasets generated and/or analyzed during the current study are available in the FAERS

246 (<https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>) and JADER

247 (<https://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp>) repositories.

248

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251

252 **Ethics approval**

253 Not applicable because spontaneous reports of the FAERS and JADER are anonymous and

254 public.

255

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Figure legends

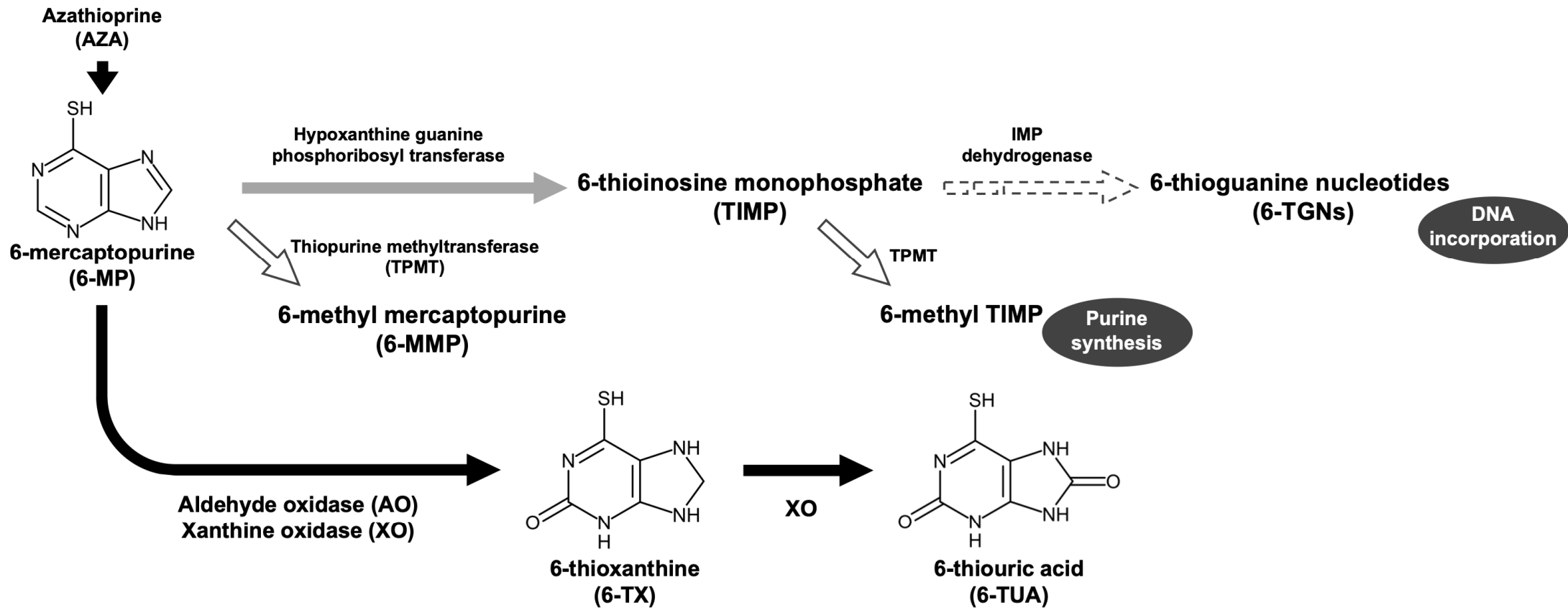
Fig. 1 Anabolic and catabolic pathway of 6-mercaptopurine metabolism.

Fig. 2 The number of reports and ROR for the hematological disorders from FAERS. The dotted gray line represents upper limit of ROR_{AZA} score. ROR_{AZA} and each ROR_{AO} inhibitor scores were expressed as filled square, and $ROR_{AZA \cap AO}$ inhibitor scores were expressed as open square.

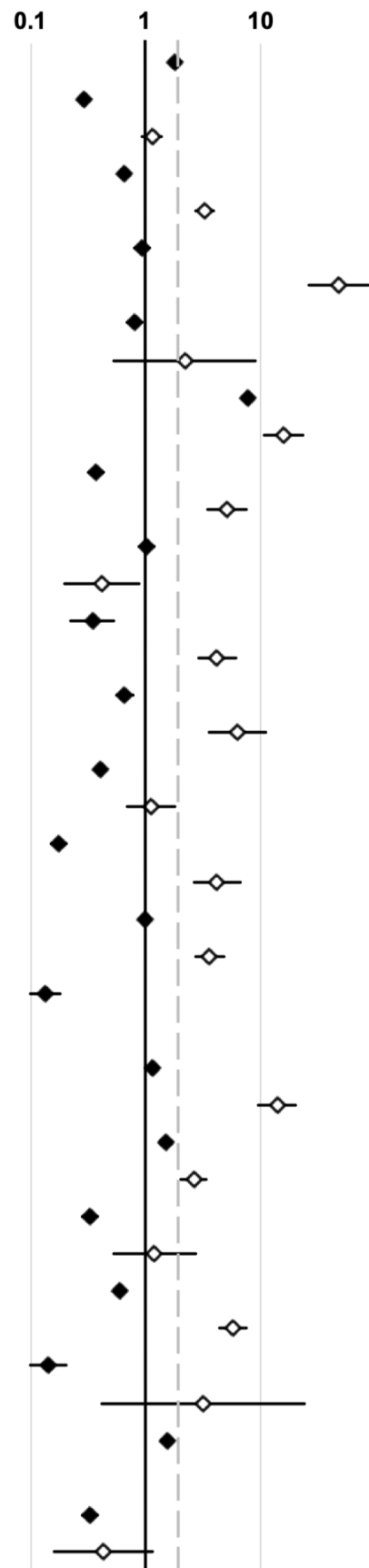
Fig. 3 The number of reports and ROR for the hematological disorders from JADER. The dotted gray line represents upper limit of ROR_{AZA} score. ROR_{AZA} and each ROR_{AO} inhibitor scores were expressed as filled square, and $ROR_{AZA \cap AO}$ inhibitor scores were expressed as open square.

Fig. 4 The number of reports and ROR for the hepatic disorders from FAERS. The dotted gray line represents upper limit of ROR_{AZA} score. ROR_{AZA} and each ROR_{AO} inhibitor scores were expressed as filled square, and $ROR_{AZA \cap AO}$ inhibitor scores were expressed as open square.

Fig. 5 The number of reports and ROR for the hepatic disorders from JADER. The dotted gray line represents upper limit of ROR_{AZA} score. ROR_{AZA} and each ROR_{AO} inhibitor scores were expressed as filled square, and $ROR_{AZA \cap AO}$ inhibitor scores were expressed as open square.



FAERS	Number of reports			ROR	95 %CI	
	Drugs	All	Hematologic disorder	Percentages of the events		
	AZA	98,419	3,411	3.47	1.81	1.75 – 1.87
	Amitriptyline	62,849	363	0.58	0.29	0.26 – 0.32
	AZA with Amitriptyline	5,142	113	2.20	1.13	0.94 – 1.36
	Amlodipine	221,736	2,781	1.25	0.64	0.62 – 0.67
	AZA with Amlodipine	2,065	126	6.10	3.26	2.72 – 3.91
	Chlorpromazine	9,683	175	1.81	0.92	0.80 – 1.07
	AZA with Chlorpromazine	43	21	48.84	47.92	26.35 – 87.14
	Clomipramine	10,323	163	1.58	0.81	0.69 – 0.94
	AZA with Clomipramine	48	2	4.17	2.18	0.53 – 8.99
	Clozapine	152,065	19,863	13.06	7.78	7.66 – 7.90
	AZA with Clozapine	147	35	23.81	15.69	10.73 – 22.93
	Cyclobenzaprine	25,719	188	0.73	0.37	0.32 – 0.43
	AZA with Cyclobenzaprine	327	30	9.17	5.07	3.48 – 7.38
	Domperidone	9,319	186	2.00	1.02	0.89 – 1.18
	AZA with Domperidone	845	7	0.83	0.42	0.20 – 0.88
	Felodipine	3,079	21	0.68	0.34	0.22 – 0.53
	AZA with Felodipine	405	31	7.65	4.16	2.88 – 6.00
	Hydralazine	13,236	171	1.29	0.66	0.57 – 0.76
	AZA with Hydralazine	126	14	11.11	6.28	3.60 – 10.94
	Loperamide	47,852	375	0.78	0.40	0.36 – 0.44
	AZA with Loperamide	834	18	2.16	1.11	0.69 – 1.77
	Loratadine	55,569	193	0.35	0.17	0.15 – 0.20
	AZA with Loratadine	262	20	7.63	4.15	2.63 – 6.55
	Metoclopramide	27,717	528	1.90	0.98	0.90 – 1.07
	AZA with Metoclopramide	765	51	6.67	3.59	2.70 – 4.76
	Nortriptyline	17,678	47	0.27	0.13	0.10 – 0.18
	AZA with Nortriptyline	175	0	0.00	0.00	
	Olanzapine	136,456	3,001	2.20	1.13	1.09 – 1.17
	AZA with Olanzapine	167	36	21.56	13.80	9.54 – 19.95
	Ondansetron	59,157	1,651	2.79	1.47	1.40 – 1.55
	AZA with Ondansetron	1,195	59	4.94	2.61	2.01 – 3.39
	Promethazine	28,138	181	0.64	0.32	0.28 – 0.38
	AZA with Promethazine	259	6	2.32	1.19	0.53 – 2.68
	Quetiapine	193,198	2,290	1.19	0.60	0.58 – 0.63
	AZA with Quetiapine	628	64	10.19	5.70	4.40 – 7.38
	Raloxifene	10,351	29	0.28	0.14	0.10 – 0.20
	AZA with Raloxifene	17	1	5.88	3.14	0.42 – 23.66
	Tamoxifen	28,923	860	2.97	1.54	1.44 – 1.65
	AZA with Tamoxifen	106	0	0.00	0.00	
	Verapamil	22,924	148	0.65	0.33	0.28 – 0.38
	AZA with Verapamil	480	4	0.83	0.42	0.16 – 1.13

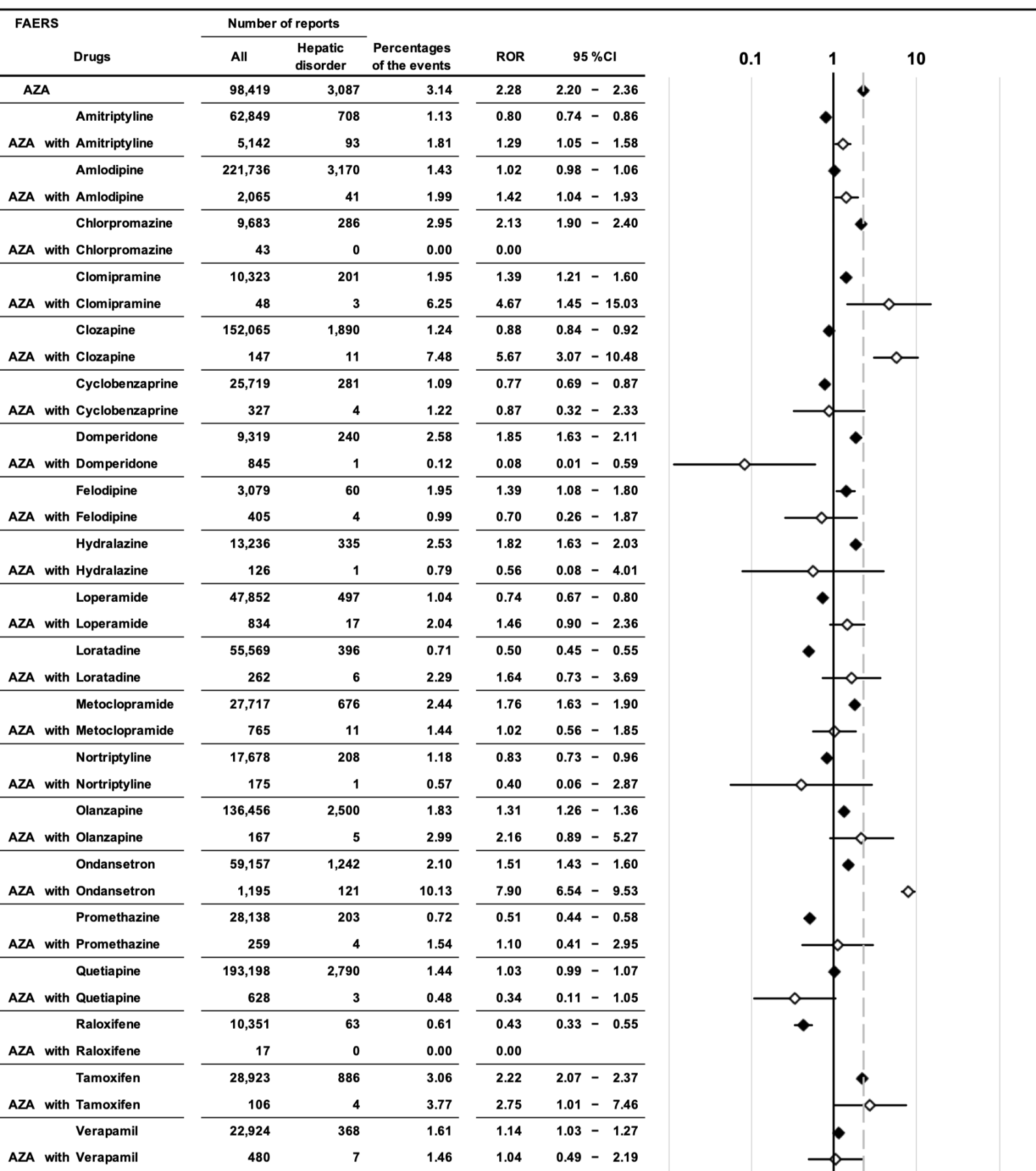


JADER		Number of reports			ROR	95 %CI	0.1	1	10
Drugs	All	Hematologic disorder	Percentages of the events						
AZA	4,713	1,107	23.49	2.77	2.59 - 2.97				
Amlodipine	8,433	491	5.82	0.55	0.50 - 0.60				
AZA with Amlodipine	128	47	36.72	5.21	3.64 - 7.47				
Domperidone	864	38	4.40	0.42	0.30 - 0.58				
AZA with Domperidone	14	4	28.57	3.59	1.13 - 11.46				
Hydralazine	238	5	2.10	0.19	0.08 - 0.47				
AZA with Hydralazine	17	2	11.76	1.20	0.27 - 5.24				
Loperamide	340	30	8.82	0.87	0.60 - 1.27				
AZA with Loperamide	34	6	17.65	1.92	0.80 - 4.65				
Loratadine	604	17	2.81	0.26	0.16 - 0.42				
AZA with Loratadine	15	1	6.67	0.64	0.08 - 4.88				
Metoclopramide	1,560	75	4.81	0.46	0.36 - 0.58				
AZA with Metoclopramide	31	4	12.90	1.33	0.47 - 3.80				
Quetiapine	4,914	168	3.42	0.32	0.27 - 0.37				
AZA with Quetiapine	9	3	33.33	4.49	1.12 - 17.96				
Verapamil	877	20	2.28	0.21	0.13 - 0.33				
AZA with Verapamil	12	1	8.33	0.82	0.11 - 6.33				

0.1

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JADER		Number of reports		Percentages of the events	ROR	95 %CI			
Drugs	All	Hepatic disorder					0.1	1	10
AZA	4,713	316	6.70	1.25	1.11 - 1.40				
Amlodipine	8,433	792	9.39	1.82	1.69 - 1.96				
AZA with Amlodipine	128	6	4.69	0.85	0.38 - 1.93				
Domperidone	864	135	15.63	3.22	2.68 - 3.87				
AZA with Domperidone	14	0	0.00	0.00					
Hydralazine	238	13	5.46	1.00	0.57 - 1.75				
AZA with Hydralazine	17	4	23.53	5.33	1.74 - 16.35				
Loperamide	340	26	7.65	1.44	0.96 - 2.14				
AZA with Loperamide	34	2	5.88	1.08	0.26 - 4.52				
Loratadine	604	88	14.57	2.96	2.36 - 3.71				
AZA with Loratadine	15	1	6.67	1.24	0.16 - 9.41				
Metoclopramide	1,560	86	5.51	1.01	0.81 - 1.26				
AZA with Metoclopramide	31	1	3.23	0.58	0.08 - 4.24				
Quetiapine	4,914	234	4.76	0.87	0.76 - 0.99				
AZA with Quetiapine	9	0	0.00	0.00					
Verapamil	877	69	7.87	1.48	1.16 - 1.89				
AZA with Verapamil	12	2	16.67	3.47	0.76 - 15.82				

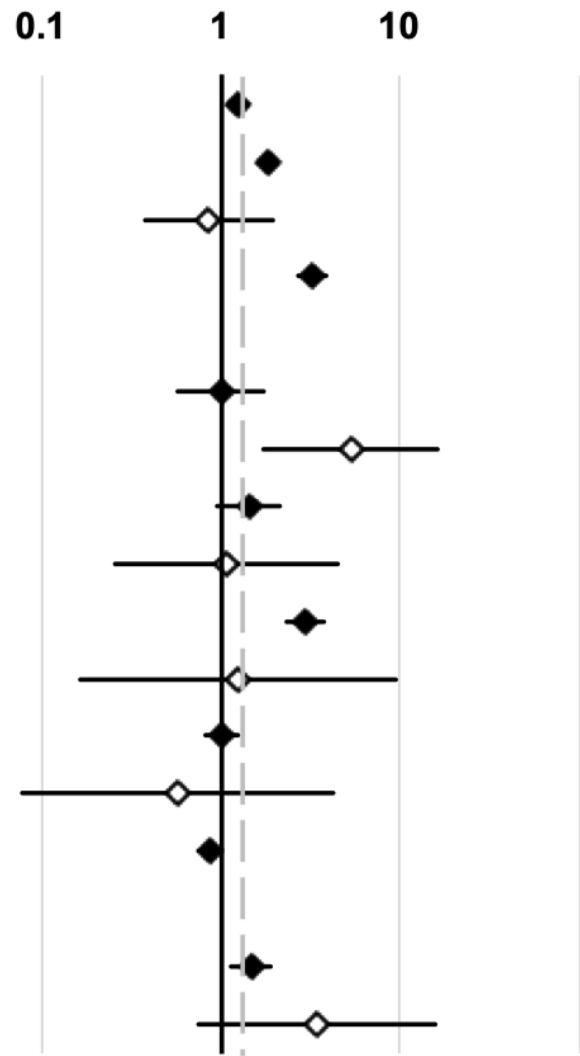


Table 1. The ratio of AO inhibitory effects to clinical blood concentrations.

Compounds	$C_{\max}$ (μM)		IC_{50} (μM)	$C_{\max}/\text{IC}_{50}$
Raloxifene	0.0034	(For women receiving 60 mg/day for 14 days)	0.0029	1.18
Chlorpromazine	0.47	(For patients receiving 100 mg/day for 30 days)	0.57	0.82
Clozapine	3.49	(For patients receiving 300 mg/day for 8 days)	4.4	0.79
Amitriptyline	0.14	(For patients receiving 75 mg/day for more than 14 days)	0.26	0.53
Quetiapine	0.45	(For patients receiving 200 mg/day for more than 3 days)	1.4	0.32
Clomipramine	0.08	(For adult volunteers receiving 50 mg)	0.48	0.16
Tamoxifen	0.20	(For patients receiving 20 mg/day for 28 days)	2.2	0.09
Nortriptyline	0.06	(For adult volunteers receiving 25 mg)	0.85	0.07
Promethazine	0.03	(For adult volunteers receiving 75 mg)	0.51	0.07
Felodipine	0.02	(For adult volunteers receiving 5 mg)	0.30	0.06
Verapamil	0.18	(For adult men receiving 80 mg)	3.5	0.05
Cyclobenzaprine	0.09	(For adult volunteers receiving 10 mg)	3.1	0.03
Loratadine	0.01	(For adult volunteers receiving 10 mg)	0.49	0.02
Olanzapine	0.09	(For adult volunteers receiving 5 or 10 mg/day for 8 days)	6.0	0.01
Ondansetron	0.03	(For adult volunteers receiving 4 mg)	2.1	0.01
Domperidone	0.03	(For adult volunteers receiving 10 mg)	3.0	0.01
Metoclopramide	0.18	(For adult volunteers receiving 20 mg)	31	0.01
Amlodipine	0.01	(For adult men receiving 5 mg)	5.5	0.00
Loperamide	0.00	(For adult volunteers receiving 2 mg)	10	0.00

IC_{50} values were based on previously reported phthalazine oxidation assays (Obach et al., 2004). Blood concentrations were obtained from the package inserts of each drug.

Table S1. Drug combinations with hematologic disorder signals detected using the Ω shrinkage measure model in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) analysis.

Combination of drugs			Number of reports		Ω	$\Omega_{0.25}$
			Hematologic disorder	Other adverse effects		
Azathioprine	and	Amlodipine	126	1939	0.84	0.58
Azathioprine	and	Chlorpromazine	21	22	3.82	2.82
Azathioprine	and	Clozapine	35	112	0.74	0.25
Azathioprine	and	Cyclobenzaprine	30	297	1.41	0.86
Azathioprine	and	Felodipine	31	374	1.15	0.61
Azathioprine	and	Hydralazine	14	112	1.68	0.82
Azathioprine	and	Loratadine	20	242	1.14	0.47
Azathioprine	and	Metoclopramide	51	714	0.95	0.54
Azathioprine	and	Olanzapine	36	131	2.55	1.99
Azathioprine	and	Quetiapine	64	564	1.57	1.20

Table S2. Drug combinations with hepatic disorder signals detected using the Ω shrinkage measure model in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) analysis.

Combination of drugs	Number of reports		Ω	Ω_{025}
	Hepatic disorder	Other adverse effects		
Azathioprine and Clozapine	11	136	1.17	0.32
Azathioprine and Ondansetron	121	1074	1.49	1.23