

Susceptibility to adverse drug reactions

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1 **Susceptibility to adverse drug reactions**

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30

31 **Abstract**

32 The pharmacological effects of a drug depend on its concentration at the site of action, and
33 therefore on the concentration in blood and on the dose. The relationship between the
34 concentration or dose and the corresponding effect can usually be represented
35 mathematically as a rectangular hyperbola; when effect is plotted against log concentration
36 or log dose, the curve is sigmoidal.

37 Inevitably, the effect size and the doses causing benefit and harm will differ among
38 individuals, since they are biological phenomena: some are more likely than others to suffer
39 harm at any given dose. Some harmful effects can occur at much lower doses than those
40 used in therapeutics; that is, the log dose–response curve for harm lies far to the left of the
41 log dose–response curve for benefit. Those who suffer such reactions are *hypersusceptible*.
42 When the dose–response curves for harm and therapeutic effect are in the same range, dose
43 cannot separate the harmful effects from the therapeutic effects, and adverse reactions are
44 *collateral*. *Toxic* effects occur when harmful doses are above the doses needed for benefit.

45 In this review we consider factors that influence a subject’s susceptibility to adverse drug
46 reactions. Determinants of susceptibility include **I**mmunological, **G**enetic, demographic
47 (**A**ge and **S**ex), **P**hysiological and **E**xogenous factors (drug–drug interactions, for example),
48 and **D**iseases and disorders such as renal failure, giving the mnemonic **I GASPED**. Some
49 susceptibility factors are discrete (for example, ‘all-or-none’) and some are continuous;
50 susceptibility can therefore be discrete or continuous; and the factors can interact to
51 determine a person’s overall susceptibility to harm.

52

53

54 **Introduction**

55 Some patients become ill from a dose of a drug which in other patients has no discernible
56 effect; some patients die from exposure to drugs that are safe and effective in other patients.

57 There are in effect two distinct types of adverse drug reaction (ADR): those that will
58 affect all patients, but which occur at different doses in different patients; and those that will
59 affect some patients, but not all, however large a dose is administered. The response in
60 affected patients will necessarily depend on dose; it is a misconception that immunological
61 reactions such as anaphylaxis [¹] are unrelated to dose, although the dose-dependence may
62 not be evident within the therapeutic dose range.

63 In this review we consider the factors that influence the susceptibility of subjects to
64 ADRs. Our review derives primarily from a lecture at the British Pharmacological Society's
65 *Pharmacology 2018* meeting and updates a review of the harms from medicines.[²]

66 **The dose of the drug**

67 The premise on which this review is based is that all pharmacological effects are related to
68 the concentration of a pharmacological agent at its site or sites of action, whether the action
69 is beneficial or detrimental. We have discussed the reasons for this, and its consequences,
70 elsewhere.[^{3,4}] The concentration at the site of action is related, in turn, to the dose
71 administered. Since the dose is usually known, while the concentration at the site of action
72 may be difficult or impossible to measure, it is often convenient to discuss dose–response
73 rather than concentration–response.

74 The key developments in the history of ideas about dose-responsiveness date from early
75 in the 20th century, although there is a prehistory.[⁵] The cumulative dose of salicylate at
76 which patients with rheumatic disease demonstrated symptoms and signs of toxicity was
77 established before the First World War.[⁶] AJ Clark used the data to draw a sigmoid log
78 dose–response curve[Figures 1 and 2,].[⁷]

79

80 | {Figures 1 and 2_near here}

81

82 The therapeutic dose of salicylate was limited by toxicity. In Hanzlik's practice, 'the
83 salicylate is given in doses of from 10 to 20 grains every hour until symptoms of
84 intoxication begin to appear.' [⁶] Dosing to toxicity has been largely abandoned outside
85 oncology.[Reference to Professor Martin's paper] While toxic ADRs are important, harm
86 can occur with therapeutic doses rather than toxic doses.[⁸] For example, constipation is a

87 collateral adverse reaction to opioid analgesia, and is expected to accompany the therapeutic
88 action. Where the dose–response curve for a significant ADR approaches a maximum at
89 concentrations lower than those used in treating disease, we have characterized it as
90 indicating hypersusceptibility to the adverse effect in comparison with the therapeutic effect.
91 Most such ADRs affect only a small subset of the treated population—the drug would be of
92 limited clinical value if it often caused significant harm before any benefit was realized.

93 **The time-course of administration**

94 A second factor that influences the risk of adverse drug reactions is the time-course of
95 exposure in relation to the reaction. This is partly because cumulative dose is a function of
96 time, and the cumulative dose determines the risk of some ADRs. For example, the risk of
97 delayed anthracycline-induced cardiomyopathy increases with cumulative dose.[⁹]

98 The rate of change of drug concentration can also be important. Examples are the
99 development of flushing and wheeze with rapid infusion of acetylcysteine.[¹⁰]

100 **Susceptibility factors related to the patient**

101 Dose–response and time-course represent aspects of the drug and its administration.
102 Susceptibility characterizes the contribution of patient factors to the risk of an ADR. The
103 interactions between dose, time-course, and susceptibility can help clinicians understand,
104 predict, and mitigate ADRs. ‘The major interacting factors influencing the response of the
105 host to the drug’ were set out a 1958 review of untoward reactions to penicillin. The factors
106 in the ‘responding system’ included, for example, age, sex, hereditary factors, and the
107 ‘presence or stage of pathological conditions.’[¹¹]

108 ***Immunological factors***

109 Gell & Coombs classified immunological reactions into four types, each of which can be
110 associated with ADRs. Immediate (Type I) hypersensitivity reactions, in which antigen
111 binds to specific IgE, result in the degranulation of mast cells and the release of histamine,
112 bradykinin, and other mediators that cause the potentially fatal clinical syndrome of airways
113 compromise, hypovolaemia, and cardiovascular collapse. Anaphylaxis to β -lactam
114 antibiotics is an example. In the earliest reported case, a reaction to 15 000 units
115 benzylpenicillin injected intramuscularly in a soldier previously sensitized by dermal
116 application, the reaction was milder and of shorter duration after a further injection of 100
117 units subcutaneously; oral administration of benzylpenicillin produced desensitization.[¹²]
118 As far back as 1909, Anderson & Rosenau demonstrated that there was a minimum
119 sensitizing dose of horse serum globulins in the guinea pig [¹³]; recent studies in patients

120 sensitized to trinitrophenol showed a clear relation between the dose of trinitrophenol–
121 bovine serum albumin and the intensity of the anaphylactic response.[¹⁴]

122 Haemolytic anaemia provides an example of a drug-induced Type II immunological
123 reaction mediated by IgG. The drug can act as a hapten covalently bound to proteins on the
124 red cell membrane, as happens with penicillin; or can induce a Coombs' test positive
125 haemolytic anaemia by suppressing immune regulation, as happens with the checkpoint
126 inhibitors nivolumab, pembrolizumab, and ipilimumab.[¹⁵] The proportion of patients who
127 develop a positive Coombs' test with the antihypertensive drug α -methyldopa increases with
128 increasing dose.[¹⁶]

129 Serum sickness—fever, urticaria, and joint pain following injection of foreign protein—
130 was first delineated in 1905 in patients treated with horse serum containing antibody against
131 diphtheria, used for passive immunization.[¹⁷] This Type III immunological reaction is the
132 consequence of circulating immune complexes. It can occur with modern biological therapy
133 such as rituximab, a murine–human chimeric monoclonal antibody directed against the B
134 cell surface marker [CD20](#). [¹⁸]

135 Delayed-type (Type IV) immunological reactions are cell-mediated. The proportion of
136 subjects sensitized by the chemical dinitrochlorobenzene, which induces delayed-type
137 hypersensitivity, increases as the sensitizing dose increases [Figure 3a]; and in sensitized
138 individuals, the size of dermal response depends on the dose used to elicit it.[Figure 3b ¹⁹]
139 There appears to be a predisposition to being sensitized by topical allergens: patients with
140 positive patch tests to many allergens are more easily sensitized to dinitrochlorobenzene
141 than patients with no positive patch tests.[²⁰]

142

143 {Figures 3a and 3b near here}

144

145 *Genetic factors*

146 Genetic factors can determine the pharmacokinetics of drugs. It was established in the 1940s
147 that the hydrolysis of atropine by rabbit serum was determined by a gene called As;
148 hydrolysis was faster in homozygotes than heterozygotes, and absent if the As gene was
149 absent.[²¹] Prolonged apnoea from respiratory muscle paralysis in patients given the muscle
150 relaxant succinylcholine (suxamethonium) is also genetically determined. In homozygous
151 normal subjects, the drug is rapidly metabolized by an enzyme, [butyrylcholinesterase](#),
152 whose activity is impaired in those with prolonged apnoea and in their families.[²²] The
153 duration of apnoea depends on the dose in both normal and abnormal subjects, but in the

154 latter the dose-response curve is shifted far to the left [Figure 4].^[23] The ClinVar database
155 now lists 118 genetic variants of butyrylcholinesterase, of which three-quarters are
156 pathogenic or likely to be pathogenic.^[24]

157

158 {Figure 4 near here}

159

160 Pharmacodynamic differences can also be genetically determined. For example, aspirin-
161 exacerbated respiratory disease (asthma, nasal polyps, and aspirin sensitivity: Samter's
162 triad) was recognized to be familial in the 1950s; it is associated with genetic abnormalities,
163 usually in the production or action of cysteinyl leukotrienes.^[25] Another pharmacodynamic
164 susceptibility recognized in the 1950s was haemolytic anaemia with oxidizing agents. The
165 resistance of haemoglobin in red blood cells to oxidation depends on the function of
166 glucose-6-phosphate dehydrogenase, the key enzyme in the generation of reduced
167 glutathione.^[26] Over 300 enzyme variants from G6PD AACHEN to G6PD ZHITOMIR are
168 now recognized.^[27] The extent of haemolysis depends on both the enzyme variant and the
169 dose of oxidizing agent.

170 Genetic and immunological susceptibility interact through human lymphocyte-associated
171 antigens. For example, Genetic and immunological susceptibility interact through human
172 lymphocyte-associated antigens. For example, the demonstration that abacavir binds to and
173 alters the antigen coded for by HLA-B*5701, so that it alters the repertoire of peptides
174 recognized by the receptor, which now reacts to peptides previously recognized as self, and
175 causes an immune response and tissue damage. This helps to explain the observation that
176 serious cutaneous adverse reactions to abacavir are much commoner in subjects with that
177 genotype.^[28,29]

178 **Age**

179 Some ADRs are more common in infants and children, who have immature physiological
180 systems, and others are increased in the elderly with failing physiological systems and
181 increasing frailty and co-morbidity. The classical example in neonates is 'grey baby
182 syndrome.' In this syndrome, high concentrations of chloramphenicol accumulate as a result
183 of poorly developed hepatic metabolism.^[30] The high chloramphenicol concentration causes
184 cardiovascular collapse.

185 A further difficulty in children is that the range of agents is smaller than the range
186 licensed for use in adults, and it is therefore common to use preparations untested in
187 children. A study of children admitted to hospital showed that adverse reactions were more

188 likely to occur with unlicensed and off-label medicines than licensed medicines (relative
189 risk 1.67; 95% CI 1.38, 2.02; $P < 0.001$).^[31]

190 Some ADRs occur more often in older people than younger adults. For example, in
191 cross-sectional studies of French and Icelandic populations, the risk of drug-induced liver
192 injury increased four-fold from ages 15–29 to age over 70.^[32] Part of the explanation could
193 be that different populations are exposed to causative agents, such as co-amoxiclav, to
194 different extents. However, difference in exposure is not the entire explanation: the risk of
195 liver injury with flucloxacillin was 25 times higher in those aged 70–79 than in those aged
196 18–49 ^[33]; and age and dosage were independent risk factors for statin-induced liver injury
197 in a Chinese cohort.^[34] More generally, a model based on data from 1408 inpatients
198 identified age as a major predictor of preventable harm from medicines,^[35] as did several
199 other models.^[36 37]

200 Responses to drugs can differ qualitatively with age. A good example is the difference in
201 ADRs to the dopamine antagonist metoclopramide. The risk of acute dystonic–dyskinetic
202 reactions was more than thirty times greater in those below the age of 20 years than those
203 above the age of 65 years; parkinsonism was significantly commoner in those aged over 65
204 years than in those below 65.^[38] The difference may be due to the change in the balance
205 between dopamine D1 and D2 receptors with age.

206 Reduced renal function and altered body composition in older people can cause marked
207 changes in drug disposition, which probably contribute to higher rates of hospital admission
208 for ADRs.^[39] Two important sequelae to physical and mental frailty are falls (and their
209 consequence—femoral fractures) and delirium. Falls are associated with prescription of
210 hypnotics and sedatives;^[40] although benzodiazepines are particularly incriminated, the
211 regular use of a non-benzodiazepine hypnotic (‘z-drug’) increased the relative risk of falls
212 four-fold in a longitudinal study of nursing home residents.^[41] In another study, older adults
213 who continued taking drugs that were believed to increase the risk of falls were ten times
214 more likely to suffer falls than older adults who stopped taking such drugs.^[42] Opioid
215 analgesics, benzodiazepines, anticholinergic drugs, and other commonly used medicines,
216 often cause delirium in older people.^[39,43]

217 Multi-morbidity, the simultaneous occurrence of several morbid conditions, increases the
218 risk that the pharmacokinetics or effect of one or more medicines is altered by the presence
219 of disease. It also makes polypharmacy more likely, and that increases the risk of drug–drug

220 interactions. The number of possible two-way interactions* increases from 1 with 2 drugs to
221 10 with 5 drugs, to 45 with 10 drugs, to 105 with 15 drugs [Figure 5].

222

223 {Figure 5 near here}

224

225 *Sex*

226 Some adverse drug reactions are limited to one sex for biological reasons. For example,
227 clear-cell carcinoma of the vagina, a delayed consequence of exposure to diethylstilboestrol
228 *in utero*,^[44] can only occur in women. A contemporary example is the risk of abnormal
229 vaginal bleeding in women treated with anticoagulants. This is a particular problem with
230 direct-acting oral anticoagulants.^[45] In one analysis, this ‘occurred frequently (9–15/100
231 [patient-years]) and significantly more often in women of reproductive age receiving
232 edoxaban compared with women receiving warfarin.’^[46]

233 Many studies show that, for ADRs that occur in both men and women, the risk is
234 generally higher in women. For example, in a review of studies of ADRs causing or
235 occurring during admission to hospital, 8/15 studies identified female sex as a risk factor,
236 and no trial identified an increased risk in males.^[37] In an analysis of 48 cohort studies of
237 newly marketed drugs used in general practice the overall age-standardized relative risk of
238 an ADR being recorded was 1.6 (95% CI 1.5 1.7) in women.^[47] This may be partly due to
239 the use of standard doses unrelated to body size, since women are on average smaller than
240 men. Some ADRs are twice as common in women as in men. In the case of the potentially
241 fatal arrhythmia *torsade de pointes*, one factor is the sex difference in repolarization of heart
242 muscle, reflected in a longer corrected QT interval in women at baseline.^[48] Database
243 studies suggest that cough with [angiotensin-converting enzyme](#) (ACE) inhibitors is
244 approximately twice as common in women as in men, although angioedema from ACE-
245 inhibitors, whose pathogenesis is likely to be similar, is reported 30% more frequently in
246 men.^[49]

247 *Physiological changes*

248 Pregnancy has a marked influence on body composition and physiological function, and
249 hence on drug disposition. It also exposes the unborn fetus to potentially harmful
250 concentrations of maternal drugs. Wilson noted that the susceptibility of the conceptus to
251 teratogens depended on genotype, the developmental stage at the time of exposure, and the

* ${}_n C_2 = n! / (n-2)! 2! = n(n-1) / 2$

252 dose of the teratogen.^[50] The relationship between dose and response was clearly shown in
253 Himalayan rabbits exposed to thalidomide, in whom the incidence of defects in leg bones,
254 malformation of the digits, and sternal synostosis were all dose-related.^[51] The degradation
255 of a transcription factor called SALL4 has been implicated in the harm caused by
256 thalidomide, which resembles the Duane Radial Ray Syndrome that results from loss-of-
257 function mutations in the gene coding for SALL4.^[52] There are mutations in the zinc-finger
258 domain of murine SALL4 that protect it from the action of thalidomide, and explain why
259 mice are not susceptible to thalidomide embryopathy.

260 Circadian rhythm influences both the disposition of drugs and their effects. In one study,
261 unfractionated heparin was given at constant rate by infusion pump. The activated partial
262 thromboplastin time and Factor Xa inhibition assay nevertheless showed peak values
263 (towards midnight) 40% higher than trough values (towards 07.00 hours).^[53] In healthy
264 male volunteers, the clearance of an intravenous dose of 20 mg methylprednisolone given at
265 08.00 h was substantially slower than the clearance of an identical dose given at 16.00 h.^[54]
266 Both sex and genetics substantially influence chronopharmacology, at least in mice.^[55] It is
267 also possible that the menstrual cycle influences drug metabolism and hence the risk of
268 ADRs. The activity of drug-metabolizing enzymes CYP1A2, CYP2A6, and NAT2 differed
269 significantly between the early and late follicular phase in women of childbearing age, as
270 assessed by caffeine metabolism.^[56] However, since caffeine metabolite ratios were used to
271 determine enzyme activity, the results for the three enzymes were not independent.

272 *Exogenous factors*

273 Environmental factors and exposure to foodstuffs and interacting medicines are likely to
274 influence the risk of ADRs to drugs.

275 For example, patch test responses to piperazine depended on environmental
276 temperature.^[57] The authors of a Swedish study concluded that warm weather increased the
277 risk of drug-induced hyponatremia, ^[58] and ‘heat-related’ adverse effects of diuretics and
278 some other drugs were twice as frequent in summers affected by heat-waves as in control
279 summers.^[59]

280 Foodstuffs can provoke reactions analogous to those caused by medicines, as is the case
281 with tartrazine in patients with aspirin-exacerbated respiratory disease.^[60] Foodstuffs and
282 medicines can have pharmacodynamic interactions, as do ethanol and diazepam;^[61] or
283 pharmacokinetic interactions, as happens when mono-amine oxidase inhibitors prevent the
284 breakdown of tyramine from foods such as blue cheese.^[62] They can also display

285 pharmaceutical interactions, as when the absorption of tetracycline is reduced by binding to
286 calcium in milk.^[63]

287 Drug–drug interactions are well established, and an important cause of avoidable
288 ADRs.^[64] However, there is the serious difficulty, both in general and in individual
289 patients, that while potential adverse drug reactions are very numerous serious adverse
290 reactions are rare, even when they are known to occur. For example, in one study of elderly
291 Italian patients, the number of potentially important adverse drug reactions was 12578, but
292 only 464 (4%) of these were observed, and even for the most serious potential reactions,
293 only 5% resulted in clinically significant effects.^[65] This divergence between theory and
294 clinical observation suggests that the theory needs refinement.

295 *Disease*

296 Disease can affect the absorption, distribution, metabolism, and elimination of drugs.

297 The effects of renal and hepatic impairment are well known, and *Summaries of Product*
298 *Characteristics* give advice on dosage adjustment, although not all such advice may be
299 based on good evidence. The effects in liver and renal disease are, for the most part, caused
300 by higher drug concentrations. In the case of liver disease, this can be a result of porta-
301 systemic shunting, which allows orally administered agents to be absorbed without
302 undergoing first-pass hepatic metabolism; or reduced hepatic elimination as a consequence
303 of reduced metabolism or diminished biliary excretion. In kidney disease, the major effect is
304 on renal drug elimination, but some drugs—notably insulin and 25-
305 hydroxycholecalciferol—are affected by a reduction in renal metabolism.
306 Pharmacodynamic effects of liver failure are most obvious in patients with cirrhosis, who
307 are especially sensitive to sedative drugs. It is postulated that the sensitivity is related to an
308 increase in GABA-ergic tone, perhaps because of circulating endogenous benzodiazepines;
309 this is in keeping with the observation that flumazenil can sometimes lighten hepatic coma.
310 ^[66].

311 The influence of other conditions is less well explored. For example, the effects of
312 obesity on drug distribution are of increasing importance as the average body-mass index
313 increases. A recent review of vancomycin dosing noted that no recommendations make
314 adjustment for obesity, despite adjustments for actual body weight, renal function, and other
315 relevant parameters.^[67]

316 The interactions between diseases and the actions of medicines are also important, as is
317 evident, for example, in the hyperglycaemic action of corticosteroids in patients with

318 diabetes; even local corticosteroid injections cause a transient increase in blood glucose
319 concentration.[⁶⁸]

320 **Conclusions**

321 The many factors that influence the occurrence of adverse drug reactions can be
322 summarized as **D**ose, **T**ime, and **S**usceptibility (**DoTS**), reflecting properties of the drug, the
323 reaction, and the patient. The factors that alter an individual's susceptibility include
324 **I**mmunological and **G**enetic factors, **A**ge, **S**ex, **P**hysiological changes, **E**xogenous
325 influences, and **D**isease conditions; that is, **I GASPED**. Interactions between these factors
326 help to explain why some patients suffer serious adverse reactions while others are
327 unaffected; and all depend on dose of the drug.

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334

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Legends to figures

Figure 1: Cumulative percentage of patients who have become salicylate-toxic plotted against log dose of salicylate (in grains; 1 grain \simeq 65 mg) [after references 6 and 7]

Figure 2. Hanzlik's data⁶ plotted as a cumulative distribution curve (cumulative percentage versus standard deviation from a mean dose of 186 grains)

Figure 3a. Percentage of subjects sensitized -v- dose of dinitrochlorobenzene on a logarithmic scale [after reference 19]

Figure 3b. Wheal thickness response to topical dinitrochlorobenzene versus dose of dinitrochlorobenzene on a logarithmic scale in subjects sensitized to DNCB [after reference 19]; note that the dose required to provoke a response is two orders of magnitude less than the dose required to sensitize a subject

Figure 4. Duration of apnoea (minutes) -v- dose of suxamethonium in milligrams (log scale) for normal subjects (UU) and those with two abnormal alleles (AA) [after reference 23].

Figure 5: The number of pair-wise interactions of n drugs, two at a time.